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(54) Title: RENIN INHIBITORY PEPTIDES HAVING NOVEL C-TERMINAL MOIETIES			
(57) Abstract Novel renin-inhibiting peptides of formula (I): X-A ₆ -B ₇ -C ₈ -D ₉ -E ₁₀ -F ₁₁ -V. More particularly the present invention provides renin-inhibiting peptides of the formula (I), wherein A ₆ , B ₇ , C ₈ and D ₉ may represent amino acid residues; E ₁₀ and F ₁₁ may represent the 1,4-diamino-1,4-disubstituted-3-hydroxybutane or other stable transition state moieties; X is a terminal group and V is a novel terminal group. Such inhibitors are useful for the diagnosis and control of renin-dependent hypertension.			
<p>NEW RENIN INHIBITORY PEPTIDES + NONCLEAVABLE HAVE NONCLEAVABLE TRANSITION STATE INSERT CORRESP. TO THE 10,11-POSITION OF THE RENIN SUBSTRATE 10-A12C B(6-D1, 7-H, 10-A8, 10-A9B, <u>10-A12</u>, 10-A15, 10-A17, 10-A18, 10-A20, 10-B2B, 12-F1B, 12-F1C, 12-F5A, 12-G1B3, 12-K4)</p>			

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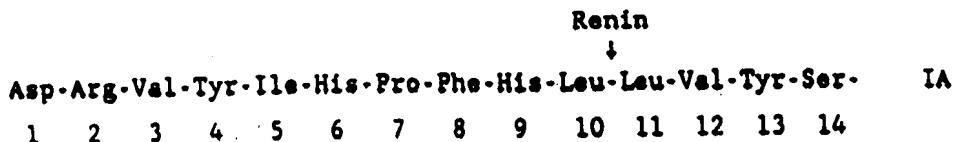
RENIN INHIBITORY PEPTIDES HAVING NOVEL C-TERMINAL MOIETIES

DESCRIPTION

BACKGROUND OF THE INVENTION

The present invention provides novel compounds. More particularly, the present invention provides renin-inhibiting peptides which have novel moieties at the C-terminus. Most particularly, the present invention provides novel renin-inhibiting peptide analogs which are derived from (1S, 3S, 4S)-1,4-diamino-1,4-disubstituted-3-hydroxy-butane. The present invention also provides renin-inhibitory compounds containing a C-terminal hydroxamate function as compared to the renin substrate. The renin inhibitors provided herein are useful for the diagnosis and control of renin-dependent hypertension.

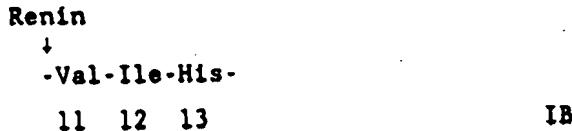
Renin is an endopeptidase which specifically cleaves a particular peptide bond of its substrate (angiotensinogen), of which the N-terminal sequence in equine substrate is for example:



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as found by L.T. Skeggs et al, J. Exper. Med. 106, 439 (1957). Human renin substrate has a different sequence as recently discovered by D.A. Tewkesbury et al., Biochem. Biophys. Res. Comm. 99:1311 (1981). It may be represented as follows:

25



30 and having the sequence to the left of the arrow (↓) being as designated in formula IA above.

Renin cleaves angiotensinogen to produce angiotensin I, which is converted to the potent pressor angiotensin II. A number of angiotensin I converting enzyme inhibitors are known to be useful in the treatment of hypertension. Inhibitors of renin are also useful in the treatment of hypertension.

A number of renin-inhibitory peptides have been disclosed. Thus, U.S. patent 4,424,207, and European published applications 45,665; 104,041; and 156,322; and U.S. patent application, Serial No.

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825,250, filed 3 February 1986; disclose certain peptides with the dipeptide at the 10,11-position containing an isostere bond. A number of statine derivatives stated to be renin inhibitors have been disclosed, see, e.g., European published applications 77,028; 81,783; 5 114,993; 156,319; and 156,321; and U.S. patents 4,478,826; 4,470,971; 4,479,941; and 4,485,099. Terminal disulfide cycles have also been disclosed in renin inhibiting peptides; see, e.g., U.S. patents 4,477,440 and 4,477,441. Aromatic and aliphatic amino acid residues at the 10,11 position of the renin substrate are disclosed in 10 U.S. patent 4,478,827 and 4,455,303. C-terminal amide cycles are disclosed in U.S. patent 4,485,099 and European published applications 156,320 and 156,318. Certain tetrapeptides are disclosed in European publications 111,266 and 77,029. Further, European published application No. 118,223 discloses certain renin inhibiting 15 peptide analogs where the 10-11 peptide link is replaced by a one to four atom carbon or carbon-nitrogen link. Additionally, Holladay et al., in "Synthesis of Hydroxyethylene and Ketomethylene Dipeptide Isosteres", Tetrahedron Letters, Vol. 24, No. 41, pp. 4401-4404, 1983 disclose various intermediates in a process to prepare stereodirected 20 "ketomethylene" and "hydroxyethylene" dipeptide isosteric functional groups disclosed in the above noted U.S. Patent No. 4,424,207.

Additionally, published European Applications 45,161 and 53,017 disclose amide derivatives useful as inhibitors of angiotensin converting enzymes.

25 Certain dipeptide and tripeptides are disclosed in U.S. patents 4,514,332; 4,510,085; and 4,548,926 as well as in European published applications 128,762; 152,255; and 181,110. Pepstatin derived renin inhibitors have been disclosed in U.S. patent 4,481,192. Retro-inverso bond modifications at positions 10-11 have been disclosed in 30 U.S. patent 4,560,505 and in European published applications 127,234 and 127,235. Derivatives of isosteric bond replacements at positions 10-11 have been disclosed in European published applications 143,746 and 144,290; and U.S. patent application, Serial No. 833,993, filed 27 February 1986. Isosteric bond modifications at positions 11-12 35 and 12-13 have been disclosed in European published application 179,352. Certain peptides containing 2-substituted statine analogues have been disclosed in European published application 157,409. Certain peptides containing 3-aminodeoxystatine have been disclosed

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in European published application 161,588. Certain peptides containing 1-amino-2-hydroxybutane derivatives at positions 10-11 have been disclosed in European published application 172,346. Certain peptides containing 1-amino-2-hydroxypropane derivatives at positions 5 10-11 have been disclosed in European published application 172,347. Certain peptides containing N-terminal amide cycles have been disclosed in U.S. patent application, Serial No. 844,716, filed 27 March 1986. Certain peptides containing dihalostatine have been disclosed in PCT application, Serial No. 000,713, filed 7 April 1986.

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INFORMATION DISCLOSURE

Certain renin inhibitor compounds were disclosed by S.H. Rosenberg, et. al., at an American Chemical Society meeting in New York City on April 13-18, 1986. These peptidic compounds have a transition state moiety of the formula $-\text{NH}-\text{CH}(\text{CH}_2\text{R})-\text{CH}(\text{OH})\text{CH}_2-(\text{CH}_2)_n-\text{NH}-$, wherein n is 0 or 1. Published British patent application 2,167,759A discloses certain compounds useful for treating angiotensin related hypotension containing a moiety of the formula $\text{NHCHR}_2-\text{CHOH}-\text{CH}_2\text{N}-$. U.S. patent 4,599,198 discloses renin-inhibitor compounds having a moiety $-\text{N}-\text{CH}(\text{CH}_2\text{-cyclohexyl})-\text{CHOH}-\text{CH}_2-\text{NR}_4-$. European patent application 181,071 discloses renin inhibitor compounds having a moiety of the formula $-\text{NH}-\text{CHR}_2-\text{CHOH}-\text{CH}_2-\text{NR}_1-$.

European published applications 156,322; 114,993; and 118,223; and PCT patent application, Serial No. 002,227, filed 21 October 1986; U.S. patent application, Serial No. 825,250, filed 3 February 25 1986; PCT patent application, Serial No. 000,291, filed 13 February 1987; and PCT patent application, Serial No. 00,507, filed 13 March 1987; disclose hydroxamic acids or esters at the C-terminus.

SUMMARY OF THE INVENTION

The present invention particularly provides a renin inhibitory peptide of the formula X-A₆-B₇-C₈-D₉-E₁₀-F₁₁-V,

A renin inhibitory peptide having a noncleavable transition state insert corresponding to the 10,11-position of the renin substrate (angiotensinogen) and having a moiety of the formula V, wherein V is

- 35 (a) $-\text{C}(-\text{Y})-\text{G}_{12}-\text{H}_{13}-\text{Z}$,
- (b) $-\text{W}$,
- (c) $-\text{G}_{12}-\text{H}_{13}-\text{W}$, or
- (d) $-\text{G}_{121}-\text{H}_{131}-\text{I}_{14}-\text{Z}$;

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corresponding to positions 12 to 14 of the renin substrate;
wherein G_{12} is absent or a divalent moiety of the formula XL_4 or
 XL_{4a} ;
wherein G_{121} is absent or a divalent moiety of the formula XL_{41} or
5 XL_{4a1} ;
wherein H_{13} is absent or a divalent moiety of the formula XL_4 ;
wherein H_{131} is absent or a divalent moiety of the formula XL_{41} ;
wherein I_{14} is absent or a divalent moiety of the formula XL_5 ;
wherein W is
10 (a) R_{14} ,
(b) $-C(-Y)-CH_2-Y-R_5$,
(c) $-C(-Y)-YR_5$,
(d) $-C(-Y)(CH_2)_n-R_5$,
(e) $-C(-Y)-(CH_2)_nN-(R_4)_2$,
15 (f) $-SO_2R_5$,
(g) $-SO_2N(R_4)_2$,
(h) $-C(-Y)(CH_2)_2-SO_2R_5$,
(i) $-C(-Y)-Y-(CH_2)_2-SO_2-R_5$,
(j) $-C(-Y)-NR_4-O-R_5$,
20 (k) $-C(-NCN)NHR_4$, or
(l) $-C(-Y)(CH_2)_qC(-Y)YR_4$;
wherein each occurrence of Y may be the same or different and Y is
(a) $-O-$,
(b) $-S-$, or
25 (c) $-NR_4-$;
wherein Z is
(a) $-O-R_{10}$,
(b) $-N(R_4)R_{14}$,
(c) $-C_4-C_8$ cyclic amino, or
30 (d) $-N(R_{10})(OR_{14})$;
wherein R_2 is
(a) hydrogen, or
(b) $-CH(R_3)R_4$;
wherein R_3 is
35 (a) hydrogen,
(b) hydroxy,
(c) C_1-C_5 alkyl,
(d) C_3-C_7 cycloalkyl.

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- (e) aryl,
- (f) -Het,
- (g) $C_1\text{-}C_3$ alkoxy, or
- (h) $C_1\text{-}C_3$ alkylthio;

5 wherein R_4 at each occurrence is the same or different and is

- (a) hydrogen, or
- (b) $C_1\text{-}C_5$ alkyl;

wherein R_5 is

- (a) $C_1\text{-}C_6$ alkyl,
- (b) $C_3\text{-}C_7$ cycloalkyl,
- (c) aryl,
- (d) -Het,
- (e) 5-oxo-2-pyrrolidinyl, or
- (f) $-\text{C}(\text{CH}_2\text{OH})_3$;

15 wherein R_8 is

- (a) hydrogen,
- (b) $C_1\text{-}C_5$ alkyl,
- (c) hydroxy,
- (d) aryl,
- (e) -Het,
- (f) guanidinyl $C_1\text{-}C_3$ alkyl-,
- (g) $C_3\text{-}C_7$ cycloalkyl, or
- (h) $-(\text{CH}_2)_p\text{-}C_3\text{-}C_7$ cycloalkyl;

wherein R_9 is

25

- (a) hydrogen,
- (b) hydroxy,
- (c) amino $C_1\text{-}C_4$ alkyl-, or
- (d) guanidinyl- $C_1\text{-}C_3$ alkyl-;

wherein R_{10} is

30

- (a) hydrogen,
- (b) $C_1\text{-}C_5$ alkyl,
- (c) $-(\text{CH}_2)_nR_{16}$,
- (d) $-(\text{CH}_2)_nR_{17}$,
- (e) $C_3\text{-}C_7$ cycloalkyl,
- (f) a pharmaceutically acceptable cation,
- (g) $-(\text{CHR}_{25})\text{-CH}_2\text{-}R_{15}$, or
- (h) $-\text{CH}_2\text{-}(\text{CHR}_{12})\text{-}R_{15}$;

wherein R_{12} is $-(\text{CH}_2)_nR_{13}$;

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wherein R_{13} is

- (a) aryl,
- (b) amino,
- (c) mono-, di- or tri- C_1-C_3 alkylamino,
- 5 (d) -Het,
- (e) C_1-C_3 alkyl,
- (f) C_3-C_7 cycloalkyl,
- (g) C_2-C_5 alkenyl,
- (h) C_3-C_7 cycloalkenyl,
- 10 (i) hydroxy,
- (j) C_1-C_3 alkoxy,
- (k) C_1-C_3 alkanoyloxy,
- (l) mercapto,
- (m) C_1-C_3 alkylthio,
- 15 (n) -COOH,
- (o) -CO-O- C_1-C_6 alkyl,
- (p) -CO-O-CH₂-(C_1-C_3 alkyl)-N(C_1-C_3 alkyl)₂,
- (q) -CO-NR₂₂R₂₆,
- (r) C_4-C_7 cyclic amino,
- 20 (s) C_4-C_7 cycloalkylamino,
- (t) guanidyl,
- (u) cyano,
- (v) N-cyanoguanidyl,
- (w) cyanoamino,
- 25 (x) (hydroxy C_2-C_4 alkyl)amino,
- (y) di-(hydroxy C_2-C_4 alkyl)amino, or
- (z) -CO-NR₂₂R₂₅;

wherein R_{14} is

- (a) hydrogen,
- 30 (b) C_1-C_{10} alkyl,
- (c) -(CH₂)_n-R₁₈,
- (d) -(CH₂)_n-R₁₉,
- (e) -(CHR₂₅)-CH₂-R₁₅,
- (f) -CH₂-(CHR₁₂)-R₁₅,
- 35 (g) (hydroxy C_1-C_8 alkyl),
- (h) (C_1-C_3 alkoxy) C_1-C_8 alkyl,
- (i) -(CH₂)_n-aryl,
- (j) -(CH₂)_n-Het.

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(k) $-(CH_2)_{n+2}-R_{18}$, or(l) $-(CH_2)_{n+2}-R_{19}$;wherein R_{15} is

- (a) hydroxy,
- 5 (b) C_3-C_7 cycloalkyl,
- (c) aryl,
- (d) amino,
- (e) mono-, di-, or tri- C_1-C_3 alkylamino,
- (f) mono- or di-(hydroxy C_2-C_4 alkyl)amino,
- 10 (g) -Het,
- (h) C_1-C_3 alkoxy-,
- (i) C_1-C_3 alkanoyloxy-,
- (j) mercapto,
- (k) C_1-C_3 alkylthio-,
- 15 (l) C_1-C_3 alkyl,
- (m) C_4-C_7 cyclic amino,
- (n) C_4-C_7 cycloalkylamino,
- (o) C_2-C_5 alkenyloxy, or
- (p) C_3-C_7 cycloalkenyl;

20 wherein R_{16} is

- (a) aryl,
- (b) amino,
- (c) mono- or di- C_1-C_3 alkylamino,
- (d) hydroxy,
- 25 (e) C_3-C_7 cycloalkyl,
- (f) C_4-C_7 cyclic amino, or
- (g) C_1-C_3 alkanoyloxy;

wherein R_{17} is

- (a) -Het,
- 30 (b) C_2-C_5 alkenyl,
- (c) C_3-C_7 cycloalkenyl,
- (d) C_1-C_3 alkoxy,
- (e) mercapto,
- (f) C_1-C_3 alkylthio,
- (g) -COOH,
- (h) -CO-O- C_1-C_6 alkyl,
- (i) -CO-O- $CH_2-(C_1-C_3$ alkyl)-N(C_1-C_3 alkyl)₂,
- (j) -CO-NR₂₂R₂₆,

- (k) tri- C_1 - C_3 alkylamino,
- (l) guanidyl,
- (m) cyano,
- (n) N-cyanoguanidyl,
- 5 (o) (hydroxy C_2 - C_4 alkyl)amino, or
- (p) di-(hydroxy C_2 - C_4 alkyl)amino;

wherein R_{18} is

- (a) amino,
- (b) mono-, or di- C_1 - C_3 alkylamino,
- 10 (c) C_4 - C_7 cyclic amino, or
- (d) C_4 - C_7 cycloalkylamino;

wherein R_{19} is

- (a) aryl,
- (b) -Het,
- 15 (c) tri- C_1 - C_3 alkylamino,
- (d) C_3 - C_7 cycloalkyl,
- (e) C_2 - C_5 alkenyl,
- (f) C_3 - C_7 cycloalkenyl,
- (g) hydroxy,
- 20 (h) C_1 - C_3 alkoxy,
- (i) C_1 - C_3 alkanoyloxy,
- (j) mercapto,
- (k) C_1 - C_3 alkylthio,
- (l) -COOH,
- 25 (m) -CO-O- C_1 - C_6 alkyl,
- (n) -CO-O-CH₂-(C_1 - C_3 alkyl)-N(C_1 - C_3 alkyl)₂,
- (o) -CO-NR₂₂R₂₆,
- (p) C_4 - C_7 cycloalkylamino,
- (q) guanidyl,
- 30 (r) cyano,
- (s) N-cyanoguanidyl,
- (t) cyanoamino,
- (u) (hydroxy C_2 - C_4 alkyl)amino,
- (v) di-(hydroxy C_2 - C_4 alkyl)amino,
- 35 (w) -SO₃H, or
- (x) -CO-NR₂₂R₂₅;

wherein R_{22} is

- (a) hydrogen, or

(b) $C_1\text{-}C_3\text{alkyl}$;

wherein R_{25} is

- (a) $-(CH_2)_n\text{-}R_{13}$,
- (b) hydrogen,
- 5 (c) $C_1\text{-}C_3\text{alkyl}$, or
- (d) phenyl- $C_1\text{-}C_3\text{alkyl}$;

wherein R_{26} is

- (a) hydrogen,
- (b) $C_1\text{-}C_3\text{alkyl}$, or
- 10 (c) phenyl- $C_1\text{-}C_3\text{alkyl}$;

wherein for each occurrence n is independently an integer of zero to five inclusive;

wherein p is zero to 2, inclusive;

wherein q is 1 to 5, inclusive;

15 wherein aryl is phenyl or naphthyl substituted by zero to 3 of the following:

- (a) $C_1\text{-}C_3\text{alkyl}$,
- (b) hydroxy,
- (c) $C_1\text{-}C_3\text{alkoxy}$,
- 20 (d) halo,
- (e) amino,
- (f) mono- or di- $C_1\text{-}C_3\text{alkylamino}$,
- (g) $-\text{CHO}$,
- (h) $-\text{COOH}$,
- 25 (i) COOR_{26} ,
- (j) CONHR_{26} ,
- (k) nitro,
- (l) mercapto,
- (m) $C_1\text{-}C_3\text{alkylthio}$,
- 30 (n) $C_1\text{-}C_3\text{alkylsulfinyl}$,
- (o) $C_1\text{-}C_3\text{alkylsulfonyl}$,
- (p) $-\text{N}(R_4)\text{-}C_1\text{-}C_3\text{alkylsulfonyl}$,
- (q) SO_3H ,
- (r) SO_2NH_2 ,
- 35 (s) $-\text{CN}$,
- (t) $-\text{CH}_2\text{NH}_2$,
- (u) COOR_{25} , or
- (v) CONHR_{25} ;

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wherein -Het is a 5- or 6-membered saturated or unsaturated ring containing from one to three heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur; and including any bicyclic group in which any of the above heterocyclic rings is fused 5 to a benzene ring, which heterocyclic moiety is substituted with zero to 3 of the following:

- (i) C_1 - C_6 alkyl,
- (ii) hydroxy,
- (iii) trifluoromethyl,
- 10 (iv) C_1 - C_4 alkoxy,
- (v) halo,
- (vi) aryl,
- (vii) aryl C_1 - C_4 alkyl-,
- (viii) amino, or
- 15 (ix) mono- or di- C_1 - C_4 alkylamino;

or a carboxy-, amino-, or other reactive group-protected form; or a pharmaceutically acceptable acid addition salt thereof.

By "renin inhibitory peptide" is meant a compound capable of inhibiting the renin enzyme in mammalian metabolism and having three 20 or more amino acid residues linked by peptidic or pseudo-peptidic bonds.

By "a non-cleavable transition state insert" is meant a transition state insert which is not cleavable by a hydrolytic enzyme in mammalian metabolism. A variety of such transition state inserts, 25 corresponding to the 10,11-position of the renin substrate, are known in the art, including those disclosed in the following references:

U.S. Patent 4,424,207 (Szelke); European Patent 104041A (Szelke); European Patent Application 144,290A (Ciba Geigy AG); European Patent 0,156,322 (Merck); European Patent 161-988A (Merck); 30 European Patent 0,172,347 (Abbott); European Patent 172-346-A (Abbott); European Patent 156-318 (Merck); European Patent 157-409 (Merck); European Patent 152-255 (Sankyo); and U.S. Patent 4,548,926 (Sankyo); and

U.S. patent application, Serial No. 904,149, filed 5 September 35 1986; U.S. patent application, Serial No. 844,716, filed 27 March 1986; PCT application, Serial No. 000,713, filed 7 April 1986; U.S. patent application, Serial No. 945,340, filed 22 December 1986; and U.S. patent application, Serial No. 825,250, filed 3 February 1986;

and

A. Spaltenstein, P. Carpino, F. Miyake and P.B. Hyskins, *Tetrahedron Letters*, 27:2095 (1986); D.H. Rich and M.S. Bernatowicz, *J. Med. Chem.*, 25:791 (1982); Roger, *J. Med. Chem.*, 28:1062 (1985);
5 D.M. Glick et al., *Biochemistry*, 21:3746 (1982); D.H. Rich, *Biochemistry*, 24:3165 (1985); R.L. Johnson, *J. Med. Chem.*, 25:605 (1982);
R.L. Johnson and K. Verschovor, *J. Med. Chem.*, 26:1457 (1983); R.L.
Johnson, *J. Med. Chem.*, 27:1351 (1984); P.A. Bartlett et al., *J. Am. Chem. Soc.*, 106:4282 (1984); and *Peptides: Synthesis, Structure and*
10 *Function* (V.J. Hruby; D.H. Rich, eds.) *Proc. 8th American Peptide Sym.*, Pierce Chemical Company, Rockford, Ill., pp. 511-20; 587-590 (1983).

As is apparent to those of ordinary skill in the art, the renin inhibitory peptides of the present invention can occur in several 15 isomeric forms, depending on the configuration around the asymmetric carbon atoms. All such isomeric forms are included within the scope of the present invention. Preferably, the stereochemistry of the amino acids corresponds to that of the naturally-occurring amino acids.

20 These compounds are shown in relation to the human renin substrate as follows:

6	7	8	9	10	11	12	13
-His	Pro	Phe	His	Leu	Val	Ile	His-
X	A ₆	B ₇	C ₈	D ₉	E ₁₀	F ₁₁	V

25 Examples of pharmaceutically acceptable acid addition salts include: acetate, adipate, alginate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, citrate, camphorate, camphorsulfonate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, fumarate, glucoheptanoate, glycerophosphate, hemisulfate, heptanoate, hexanoate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethanesulfonate, lactate, maleate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, oxalate, palmitate, pectinate, persulfate, 3-phenylpropionate, picrate, pivalate, propionate, succinate, tartrate, thiocyanate, tosylate, and undecanoate.

35 The carbon atom content of various hydrocarbon-containing moieties is indicated by a prefix designating the minimum and maximum number of carbon atoms in the moiety, i.e., the prefix (C_i-C_j) indicates a moiety of the integer "i" to the integer "j" carbon

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atoms, inclusive. Thus (C₁-C₄)alkyl refers to alkyl of one to 4 carbon atoms, inclusive, or methyl, ethyl, propyl, butyl, and isomeric forms thereof. C₄-C₇cyclic amino indicates a monocyclic group containing one nitrogen and 3 to 7 carbon atoms.

5 Examples of (C₃-C₁₀)cycloalkyl which include alkyl-substituted cycloalkyl, are cyclopropyl, 2-methylcyclopropyl, 2,2-dimethylcyclopropyl, 2,3-diethylcyclopropyl, 2-butylcyclopropyl, cyclobutyl, 2-methylcyclobutyl, 3-propylcyclobutyl, cyclopentyl, 2,2-dimethylcyclopentyl, and cyclohexyl.

10 Examples of aryl include phenyl, naphthyl, (o-, m-, p-)tolyl, (o-, m-, p-)ethylphenyl, 2-ethyl-tolyl, 4-ethyl-o-tolyl, 5-ethyl-m-tolyl, (o-, m-, or p-)propylphenyl, 2-propyl-(o-, m-, or p-)tolyl, 4-isopropyl-2,6-xylyl, 3-propyl-4-ethylphenyl, (2,3,4-, 2,3,6-, or 2,4,5-)trimethylphenyl, (o-, m-, or p-)fluorophenyl, (o-, m-, or 15 p-trifluoromethyl)phenyl, 4-fluoro-2,5-xylyl, (2,4-, 2,5-, 2,6-, 3,4-, or 3,5-)difluorophenyl, (o-, m-, or p-)chlorophenyl, 2-chloro-p-tolyl, (3-, 4-, 5- or 6-)chloro-o-tolyl, 4-chloro-2-propylphenyl, 2-isopropyl-4-chlorophenyl, 4-chloro-3-fluorophenyl, (3- or 4-)chloro-2-fluorophenyl, (o-, m-, or p-)trifluoro-methylphenyl, (o-, m-, or 20 p-)ethoxyphenyl, (4- or 5-)chloro-2-methoxyphenyl, and 2,4-dichloro-(5- or 6-)methylphenyl.

Examples of -Het include: 2-, 3-, or 4-pyridyl, imidazolyl, indolyl, Nⁱⁿ-formyl-indolyl, Nⁱⁿ-C₂-C₅alkyl-C(0)-indolyl, [1,2,4]-triazolyl, 2-, 4-, 5-pyrimidinyl, 2-, 3-thienyl, piperidinyl, pyrrolyl, 25 pyrrolinyl, pyrrolidinyl, pyrazolyl, pyrazolinyl, pyrazolidinyl, imidazolinyl, imidazolidinyl, pyrazinyl, piperazinyl, pyridazinyl, oxazolyl, oxazolidinyl, isoxazolyl, isoxazolidinyl, morpholinyl, thiazolyl, thiazolidinyl, isothiazolyl, isothiazolidinyl, quinolinyl, 30 isoquinolinyl, benzimidazolyl, benzothiazolyl, benzoxazolyl, furyl, thienyl, and benzothienyl. Each of these moieties may be substituted as noted above.

As would be generally recognized by those skilled in the art of organic chemistry, a heterocycle as defined herein for -Het would not be bonded through oxygen or sulfur or through nitrogen which is within a ring and part of a double bond.

"alo is halogen (fluoro, chloro, bromo, or iodo) or trifluoromethyl.

Examples of pharmaceutically acceptable cations include:

pharmacologically acceptable metal cations, ammonium, amine cations, or quaternary ammonium cations. Especially preferred metal cations are those derived from the alkali metals, e.g., lithium, sodium, and potassium, and from the alkaline earth metals, e.g., magnesium and calcium, although cationic forms of other metals, e.g., aluminum, zinc, and iron are also within the scope of this invention. Pharmacologically acceptable amine cations are those derived from primary, secondary, or tertiary amines.

The novel peptides herein contain both natural and synthetic amino acid residues. These residues are depicted using standard amino acid abbreviations (see, e.g., IUPAC-IUB Joint Commission on Biochemical Nomenclature (JCBN), "Nomenclature and Symbolism for Amino Acids and Peptides," Eur. J. Biochem. 138:9-37 (1984) unless otherwise indicated.

The renin inhibitors of this invention are useful for treating any medical condition for which it is beneficial to reduce the levels of active circulating renin. Examples of such conditions include renin-dependent hypertension, hypertension, hypertension under treatment with another antihypertensive and/or a diuretic agent, congestive heart failure, renin-dependent hyperaldosteronism, angina, post-myocardial infarction and other renin-dependent cardiovascular disorders. The renin-angiotension system may play a role in maintenance of intracellular homeostasis: see Clinical and Experimental Hypertension, 86, 1739-1742 (1984) at page 1740 under Discussion.

The compounds of the present invention are preferably orally administered to humans to effect renin inhibition for the purpose of favorably affecting blood pressure. For this purpose, the compounds are administered from 0.1 mg to 1000 mg per kg per dose, administered from 1 to 4 times daily. Equivalent dosages for other routes of administration are also employed. For example, renin-associated hypertension and hyperaldosteronism are effectively treated by the administration of from 1.0 to 50 milligrams of the compound per kilogram of body weight per day.

The exact dose depends on the age, weight, and condition of the patient and on the frequency and route of administration. Such variations are within the skill of the practitioner or can readily be determined.

The compounds of the present invention may be in the form of

pharmaceutically acceptable salts both those which can be produced from the free bases by methods well known in the art and those with which acids have pharmacologically acceptable conjugate bases.

Conventional forms and means for administering renin-inhibiting 5 compounds may be employed and are described, e.g., in U.S. Patent No. 4,424,207 which is incorporated by reference herein. Likewise, the amounts disclosed in the U.S. Patent No. 4,424,207 are examples applicable to the compounds of the present invention.

The compounds of the present invention are preferably orally 10 administered in the form of pharmacologically acceptable acid addition salts. Preferred pharmacologically acceptable salts for oral administration include the citrate and aspartate salts, although any pharmacologically acceptable salt is useful in this invention, including those listed above. These salts may be in hydrated or 15 solvated form.

For these purposes the compounds of the present invention may be administered parenterally, by inhalation spray, or rectally in dosage 20 unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles. The term parenteral as used herein includes subcutaneous injections, intravenous, intramuscular, intrasternal injection or infusion techniques. In addition to the treatment of warm-blooded animals such as mice, rats, horses, dogs, cats, etc., the compounds of the invention are effective in the treatment of humans.

25 The pharmaceutical compositions may be in the form of a sterile injectable preparation, for example as a sterile injectable aqueous or oleagenous suspension. This suspension may be formulated according to the known art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a 30 sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any 35 bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

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The peptides of this invention may also be administered in the form of suppositories for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient which is solid at ordinary temperatures but 5 liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials are cocoa butter and polyethylene glycols.

The renin-inhibiting compounds of this invention may be administered in combination with other agents used in antihypertensive 10 therapy such as diuretics, α and/or β -adrenergic blocking agents, CNS-acting agents, adrenergic neuron blocking agents, vasodilators, angiotensin I converting enzyme inhibitors, and the like as described for example in published European patent application 156,318.

The present invention is also directed to combinations of the 15 novel renin-inhibitory peptides of Formula I with one or more antihypertensive agents selected from the group consisting of diuretics, α and/or β -adrenergic blocking agents, CNS-acting agents, adrenergic neuron blocking agents, vasodilators, angiotensin I converting enzyme inhibitors, and other antihypertensive agents.

20 For example, the compounds of this invention can be given in combination with such compounds or salts or other derivative forms thereof as:

Diuretics: acetazolamide; amiloride; bendroflumethiazide; benzthiazide; bumetanide; chlorothiazide; chlorthalidone; cyclothiazide; 25 ethacrynic acid; furosemide; hydrochlorothiazide; hydroflumethiazide; indacrinone (racemic mixture, or as either the (-) or (-) enantiomer alone, or a manipulated ratio, e.g., 9:1 of said enantiomers respectively); metolazone; methylclothiazide; muzolimine; polythiazide; quinethazone; sodium ethacrynat; sodium nitroprusside; spironol. 30 acetone; ticrynaten; trimaterene; trichlormethiazide;

α -Adrenergic Blocking Agents: dibenamine; phentolamine; phenoxybenzamine; prazcsin; tolazoline;

β -Adrenergic Blocking Agents: atenolol; metoprolol; nadolol; propranolol; timolol;

35 ((\pm)-2-[3-(tert-butylamino)-2-hydroxypropoxy]-2-furananilide) (enacarolol);

(2-acetyl-7-(2-hydroxy-3-isopropyaminopropoxy)benzofuran HCl)(befunolol);

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((\pm)-1-(isopropylamino)-3-(p-(2-cyclopropylmethoxyethyl)-phenoxy)-2-propranol HCl) (betaxolol);
(1-[(3,4-dimethoxyphenethyl)amino]-3-(m-tolylloxy)-2-propanol HCl) (bevantolol);
5 (((\pm)-1-(4-((2-isopropoxyethoxy)methyl)phenoxy)-3-isopropylamino-2-propanol)fumarate) (bisoprolol);
(4-(2-hydroxy-3-[4-(Phenoxy)methyl]-piperidino)-propoxy)-indole;
(carbazolyl-4-oxy-5,2-(2-methoxyphenoxy)-ethylamino-2-propanol);
10 (1-((1,1-dimethylethyl)amino)-3-((2-methyl-1H-indol-4-yl)oxy)-2-propanol benzoate) (bopindolol);
(1-(2-exobicyclo[2.2.1]-hept-2-ylphenoxy)-3-[(1-methylethyl)-amino]-2-propanol HCl) (bornaprolol);
(o-[2-hydroxy-3-[(2-indol-3-yl-1,1-dimethylethyl)-amino]propoxy]benzonitrile HCl) (bucindolol);
15 (α -[(tert-butylamino)methyl]-7-ethyl-2-benzofuranmethanol) (bufuralol);
(3-[3-acetyl-4-[3-(tert-butylamino)-2-hydroxypropyl]-phenyl]-1,1-diethylurea HCl) (celiprolol);
((\pm)-2-[2-[3-[(1,1-dimethylethyl)amino]-2-hydroxypropoxy]phenoxy]-N-
20 methylacetamide HCl) (cetamolol);
(2-benzimidazolyl-phenyl(2-isopropylaminopropanol));
((\pm -3'-acetyl-4'-(2-hydroxy-3-isopropylaminoproxy)-acetanilide HCl)
(diacetolol);
25 (methyl-4-[2-hydroxy-3-[(1-methylethyl)aminopropoxyl]]-benzene-propanoate HCl) (esmolol);
(erythro-DL-1-(7-methylindan-4-yloxy)-3-isopropylaminobutan-2-ol);
(1-(tert-butylamino)-3-[0(2-propynyl)phenoxy]-2-propanol (pargolol);
30 (1-(tert-butylamino)-3-[o-(6-hydrazino-3-pyridazinyl)phenoxy]-2-propanol diHCl) (prizidilol);
((α)-2-hydroxy-5-[(R)-1-hydroxy-2-[(R)-(1-methyl-3-phenylpropyl)-amino]ethyl]benzamide);
35 (4-hydroxy-9-[2-hydroxy-3-(isopropylamino)-propoxy]-7-methyl-5H-furo[3,2-g][1]-benzopyran-5-one) (iprocrolool);
((α)-5-(tert-butylamino)-2-hydroxypropoxy)-3,4-dihydro-1-(2H)-raphthalenone HCl) (levobunolol);
(4-(2-hydroxy-3-isopropylamino-propoxy)-1,2-benzisothiazole HCl);
40 (4-[3-(tert-butylamino)-2-hydroxypropoxy]-N-methylisocarboxytril

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HCl);

((\pm)-N-2-[4-(2-hydroxy-3-isopropylaminopropoxy)phenyl]ethyl-N'-isopropylurea) (pafenglol);

(3-[(2-trifluoroacetamido)ethyl]amino)-1-phenoxypropan-2-ol);

5 (N-(3-(o-chlorophenoxy)-2-hydroxypropyl)-N'-(4'-chloro-2,3-dihydro-3-oxo-5-pyridazinyl)ethylenediamine);

((\pm)-N-[3-acetyl-4-[2-hydroxy-3-[(1-methylethyl)amino]propoxyphenyl]-butanamide) (acebutolol);

((\pm)-4'-[3-(tert-butylamino)-2-hydroxypropoxy]spiro[cyclohexane-10,2'-indan]-1'-one) (spirendolol);

(7-[3-[(2-hydroxy-3-[(2-methylindol-4-yl)oxylpropyl]amino)butyl]thiophylline) (teoprolol);

((\pm)-1-tert.butylamino-3-(thiochroman-8-yloxy)-2-propanol);

((\pm)-1-tert.butylamino-3-(2,3-xylyloxy)-2-propanol HCl) (xibenolol);

15 (8-[3-(tert.butylamino)-2-hydroxypropoxy]-5-methylcourmarin) (bucumolol);

(2-(3-(tert.butylamino)-2-hydroxy-propoxy)benzonitrile HCl) (bunitrolol);

((\pm)-2'-(3-(tert.butylamino)-2-hydroxypropoxy-5'-fluorobutyrophenone) 20 (butofilolol);

(1-(carbazol-4-yloxy)-3-(isopropylamino)-2-propanol) (carazolol);

(5-(3-tert.butylamino-2-hydroxy)propoxy-3,4-dihydrocarbotytil HCl) (carteolol);

(1-(tert.butylamino)-3-(2,5-dichlorophenoxy)-2-propanol) (cloranolol);

25 (1-(inden-4(or 7)-yloxy)-3-(isopropylamino)-2-propanol HCl) (indenolol);

(1-isopropylamino-3-[(2-methylindol-4-yl)oxy]-2-propanol) (mepindolol);

30 (1-(4-acetoxy-2,3,5-trimethylphenoxy)-3-isopropylaminopropan-2-ol) (metipranolol);

(1-(isopropylamino)-3-(o-methoxyphenoxy)-3-[(1-methylethyl)amino]-2-propanol) (moprolol);

((1-tert.butylamino)-3-[(5,6,7,8-tetrahydro-cis-6,7-dihydroxy-1-naphthyl)oxy]-2-propanol) (nadolol);

35 ((S)-1-(2-cyclopentylphenoxy)-3-[(1,1-dimethylethyl)amino]-2-propanol sulfate (2:1)) (penbutolol);

(4'-(1-hydroxy-2-(amino)ethyl)methanesulfonanilide) (sotalol);

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(2-methyl-3-[4-(2-hydroxy-3-tert-butylaminopropoxy)phenyl]-7-methoxy-isoquinolin-1-(2H)-one);
 (1-[4-(2-(4-fluorophenoxy)ethoxy)phenoxy]-3-isopropylamino-2-propanol HCl);
 5 ((-)-p-[3-[(3,4-dimethoxyphenethyl)amino]-2-hydroxypropoxy]- β -methyl-cinnamonicnitrile) (pacrinolol);
 ((\pm)-2-(3'-tert.butylamino-2'-hydroxypropylthio)-[5'-carbamoyl-2'-thienyl]thiazole HCl) (arotinolol);
 ((\pm)-1-[p-[2-(cyclopropylmethoxy)ethoxy]phenoxy]-3-isopropylamino)-10 2-propanol) (cicloprolol);
 ((\pm)-1-[[(3-chloro-2-methylindol-4-yl)oxy]-3-[(2-phenoxyethyl)amino]-2-propanol) (indopanolol);
 ((\pm)-6-[[2-[(3-(p-butoxyphenoxy)-2-hydroxypropyl)amino]ethyl]amino-1,3-dimethyluracil) (Ipirepolol);
 15 (4-(cyclohexylamino)-1-(1-naphtholenyloxy)-2-butanol);
 (1-phenyl-3-[2-[3-(2-cyanophenoxy)-2-hydroxypropyl]aminoethyl]hydrazo-
 toin HCl);
 (3,4-dihydro-8-(2-hydroxy-3-isopropylaminopropoxy)-3-nitroxy-2H-1-benzopyran) (nipradolol);
 20 Angiotensin I Converting Enzyme Inhibitors:
 1-(3-mercaptop-2-methyl-1-oxopropyl)-L-proline (captopril);
 (1-(4-ethoxycarbonyl-2,4(R,R)-dimethylbutanyl)indoline-2(S)-carboxylic acid);
 (2-[2-[(1-(ethoxycarbonyl)-3-phenylpropyl)amino]-1-oxopropyl]-
 25 1,2,3,4-tetrahydro-3-isoquinoline carboxylic acid);
 ((S)-1-[2-[(1-(ethoxycarbonyl)-3-phenylpropyl)amino]-1-oxopropyl]oc-
 tahydro-1H-indole-2-carboxylic acid HCl);
 (N-cyclopentyl-N-(3-(2,2-dimethyl-1-oxopropyl)thiol-2-methyl-1-oxo-
 propyl)glycine) (pivalopril);
 30 ((2R,4R)-2-(2-hydroxyphenyl)-3-(3-mercaptopropionyl)-4-thiazolidine-
 carboxylic acid);
 (1-(N-[1(S)-ethoxycarbonyl-3-phenylpropyl]-(S)-alanyl)-cis,syn-octa-
 hydroindol-2(S)-carboxylic acid HCl);
 ((-)-(S)-1-[(S)-3-mercaptop-2-methyl-1-oxopropyl]indoline-2-carboxylic
 35 acid);
 ([1(S), 4S]-1-[3-(benzoylthio)-2-methyl-1-oxopropyl]-4-phenylthio-L-
 proline;
 (3-((1-ethoxycarbonyl-3-phenyl-(1S)-propyl)amino)-2,3,4,5-tetrahydro-

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2-oxo-1-(3S)-benzazepine-1-acetic acid HCl);
(N-(2-benzyl-3-mercaptopropanoyl)-S-ethyl-L-cysteine) and the S-methyl analogue;
(N-(1(S)-ethoxycarbonyl-3-phenylpropyl)-L-alanyl-L-proline maleate)
5 (enalapril);
N-1-(S)-carboxy-3-phenylpropyl]-L-alanyl-L-proline;.
N²-(1-(S)-carboxy-3-phenylpropyl)-L-lysyl-L-proline (lisinopril);
Other Antihypertensive Agents: aminophylline; cryptenamine acetates and tannates; deserpidine; meremethoxylline procaine; pargyline; tri-methaphan camsylate; and the like, as well as admixtures and combinations thereof.

Typically, the individual daily dosages for these combinations can range from about one-fifth of the minimally recommended clinical dosages to the maximum recommended levels for the entities when they 15 are given singly. Coadministration is most readily accomplished by combining the active ingredients into a suitable unit dosage form containing the proper dosages of each. Other methods of coadministration are, of course, possible.

The novel peptides of the present invention possess an excellent 20 degree of activity in treating renin-associated hypertension and hyperaldosteronism.

The compounds of the present invention may be pharmaceutically acceptable salts both those which can be produced from the free bases by methods well known in the art and those with which acids have 25 pharmacologically acceptable conjugate bases.

The compounds of the present invention are preferably administered in the form of pharmacologically acceptable acid addition salts. Preferred pharmacologically acceptable salts for oral administration include the citrate and aspartate salts, although any 30 pharmacologically acceptable salt is useful in this invention, including those listed above. These salts may be in hydrated form.

In appropriate cases, micronization of the compounds of this invention may be advantageous for optimal drug delivery.

The compounds of the present invention are prepared as depicted 35 in the charts and as described more fully in the Preparations and Examples.

CHART A

The starting materials for the compounds of this invention are

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prepared by the Curtius rearrangement of the (2S, 4S, 5S)-5-(t-butoxycarbonylamino)-4-(t-butyldimethylsilyloxy)-2,5-disubstituted-pentanoic acids according to Chart A. (See published European patent application 173,181A, published 5 March 1986). In Chart A, V₁ is the appropriate residue necessary to prepare a final compound having a substituent within the definition of V, and all other variables are as defined above. In this process, the compounds of formula A-1 are treated with isobutyl chloroformate and triethylamine to give the mixed anhydrides (A-2) which without isolation are allowed to react with sodium azide. The resulting acyl azides (A-3) are isolated from the aqueous reaction mixture, dried and warmed with benzyl alcohol to give the carbamates A-4 via the isocyanates A-5. Both A-4 and A-5 are useful intermediates for compounds of formula I. Deprotection of the carbamates A-4 by hydrogenolysis of the benzyl moiety gives the amines A-6 which will react with activated carboxylic acids to give amides A-7, with isocyanates to give ureas A-8, with isothiocyanates to give thioureas A-9 and with chloroformates to give carbamates A-10. Guanidines A-11 are prepared by the successive reactions of the thioureas A-9 with an alkylating agent and an appropriate amine. Alternatively, the isocyanate intermediates A-5 will react with amines or alcohols to give the corresponding ureas or carbamates. The resulting intermediates can be used to prepare the compounds of formula I by the usual methods for peptide synthesis.

The process of the present invention is also more completely understood by reference to the Charts B and C. In these charts, the variables are as defined above, and in Chart C, R is defined as methyl, ethyl, phenyl or benzyl.

CHART B

Chart B describes the preparation of the fully protected peptidic acid, Bob-Phe-His(Tos)-OH, which is useful as an intermediate in the synthesis of renin inhibitors. The compound of formula B-1 is treated with p-nitrophenol and dicyclohexylcarbodiimide in ethyl acetate at 0°C for about one hour. Other activating reagents such as N-hydroxysuccimide or 1,1-carbonyldiimidazole may be utilized with condensing reagents known in the art such as diisopropylcarbodiimide, diethylphosphoryl cyanide or N-methyl-2-halopyridinium salts. Suitable solvents include tetrahydrofuran, glyme, and halocarbons such as dichloromethane and chloroform. The

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compound of formula B-2 is isolated by standard procedures known in the art.

The compound of formula B-2 is reacted with His-methyl ester hydrochloride and base in dimethylformamide at room temperature for 5 about eighteen hours. Suitable bases include hindered tertiary amines such as triethylamine or diisopropylethylamine. The compound of formula B-3 is isolated by standard procedures known in the art. The compound of formula B-3 is treated with tosyl chloride and base in methylene chloride at room temperature for about one hour. Bases 10 suitable in this transformation are similar to those described above, tertiary amines. Suitable solvents include tetrahydrofuran, ethyl acetate, diethyl ether, glyme, and halocarbons such as dichloromethane and chloroform. The compound of formula B-4 is isolated by standard procedures known in the art.

15 The compound of formula B-4 is treated with lithium hydroxide in tetrahydrofuran/water at room temperature for about thirty minutes. The compound of formula B-5 is isolated by standard procedures known in the art.

CHART C

20 Chart C illustrates the preparation of renin-inhibitory peptides containing a C-terminal hydroxamate function. The compounds of formula C-1 and C-1A are treated with a condensing reagent and base in methylene chloride at 0°C to room temperature for 30 min. to 24 hrs. Suitable solvents include tetrahydrofuran, ethyl acetate, 25 diethyl ether, glyme, and halocarbons such as dichloromethane and chloroform. Suitable bases include hindered tertiary amines such as triethylamine or diisopropylethylamine. The compound of formula C-2 is isolated by standard procedures known in the art.

30 The compound of formula C-2 is deprotected using acidic conditions. Those most commonly employed include 2:1 to 1:1 mixtures of methylene chloride/trifluoroacetic acid or dry hydrochloric acid in 1,4-dioxane or diethyl ether.

35 Condensation with the next reactant is carried out as described above. Namely, the compounds are treated with a condensing reagent and base in methylene chloride at 0°C to room temperature for 30 min. to 24 hrs. Suitable solvents include tetrahydrofuran, ethyl acetate, diethyl ether, glyme, and halocarbons such as dichloromethane and chloroform. Suitable bases include hindered tertiary amines such as

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triethylamine or diisopropylethylamine. The compound of formula C-3 is isolated by standard procedures known in the art.

This procedure may be repeated to deliver the compounds of formula C-4. The compound of formula C-4 is isolated by standard 5 procedures known in the art.

Removal of the p-toluenesulfonyl protecting group on histidine may be accomplished by nucleophilic displacement. This may be carried out with nucleophiles such as 1-hydroxybenzotriazole in protic solvents such as methanol, or with reagents such as tetra-N-10 butylammonium fluoride in aprotic solvents such as tetrahydrofuran. Times range from 30 min. to 48 hrs. at temperatures ranging from 20° to 50°C. The compound of formula C-5 is isolated by standard procedures known in the art.

Generally, the renin inhibiting polypeptides may be prepared by 15 either polymer assisted or solution phase peptide synthetic procedures analogous to those described hereinafter or to those methods known in the art. Appropriate protecting groups, reagents, and solvents for both the solution and solid phase methods can be found in "The Peptides: Analysis, Synthesis, and Biology," Vols. 1-5, eds. 20 E. Gross and T. Meienhofer, Academic Press, NY, 1979-1983; "Solid Phase Peptide Synthesis", J.M. Stewart and J.D. Young, Pierce Chemical Company, Rockford, Ill., 1984; "The Practice of Peptide Synthesis", M. Bodansky and A. Bodansky, Springer-Verlag, New York, 1984; "The Principles of Peptide Synthesis", M. Bodansky, Springer- 25 Verlag, New York, 1984. For example, the carboxylic moiety of N²-t-butyloxycarbonyl (Boc)-substituted amino acid derivatives having suitable side chain protecting groups, if necessary, may be condensed with the amino functionality of a suitably protected amino acid, peptide or polymer-bound peptide using a conventional coupling 30 protocol such as dicyclohexylcarbodiimide (DCC) and 1-hydroxybenzotriazole (HOBT) in methylene chloride or dimethylformamide. The synthetic procedures used to incorporate the novel moieties herein are also described, for example, in U.S. patents 4,424,207; 4,470,971; 4,477,440; 4,477,441; 4,478,826; 4,478,827; 4,479,941; and 35 4,485,099, which are expressly incorporated by reference herein. See, also, published European patent applications 45,161; 45,665; 53,017; 77,028; 77,029; 81,783; 104,041; 111,266; 114,993; and 118,223.

Following coupling reaction completing, the N^{α} -Boc moiety may be selectively removed with 50% trifluoroacetic acid with or without 2% anisole (v/v) in methylene chloride. Neutralization of the resultant trifluoroacetate salt may be accomplished with 10% diisopropyl-5 ethylamine or sodium bicarbonate in methylene chloride. In the case of polymer-assisted peptide synthesis, this stepwise, coupling strategy may be partially or completely automated to provide the desired peptide-polymer intermediates. Anhydrous hydrofluoric acid treatment of the peptide-polymer intermediates may then be used to 10 effect simultaneous protecting group removal and cleavage of the peptide from its polymeric support. A notable exception to this includes N^{in} -formyl-indolyl-substituted peptides in which the N^{in} -formyl-indolyl moiety is stable to TFA or hydrogen fluoride but may be removed by ammonia or sodium hydroxide. Because N^{in} -formyl-15 tryptophane (FTrp) is somewhat unstable to base in synthetic procedures, possibly causing lower yields, it may be desirable in solution phase synthesis to introduce the FTrp-containing moiety late in the synthetic sequence so that it is not exposed to such conditions.

The incorporation of N^{in} -formyl-Trp into compounds of the 20 present invention is easily accomplished because of the commercial availability of N^{α} -Boc- N^{in} -formyl-Trp-OH. However, the N^{in} -formyl moiety may be introduced into indolyl-substituted amino acid derivatives or related compounds by reaction with hydrochloric-formic acid as reported in the literature, see A. Previero et al, Biochim. 25 Biophys. Acta 147, 453 (1967); Y.C.S. Yang et al, Int. J. Peptide Protein Res. 15, 130 (1980).

Generally, methods of alkylation useful in alkylating histidine for use in the present invention are found in Cheung, S.T. et al., Can. J. Chem., Vol 55, pp. 906-910 (1977). However it is now found 30 that in the Cheung, S.T. et al, method, it is critical that the reaction conditions for the alkylation of histidine be anhydrous. Further, it is now found also that during work-up instead of adding water directly to the reaction mixture, it is preferred that a buffered aqueous solution be added to the reaction mixture, for 35 example, aqueous sodium or potassium hydrogen sulfate.

Variations in the above description for starting materials, reactants, reaction conditions and required protecting groups to obtain other such N-alkylated compounds are known to an ordinarily

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skilled chemist or are readily available in the literature.

The compounds of the present invention may be in either free form or in protected form at one or more of the remaining (not previously protected) peptide, carboxyl, amino, hydroxy, or other reactive groups. The protecting groups may be any of those known in the polypeptide art. Examples of nitrogen and oxygen protection groups are set forth in T.W. Greene, *Protecting Groups in Organic Synthesis*, Wiley, New York, (1981); J.F.W. McOmie, ed. *Protective Groups in Organic Chemistry*, Plenum Press (1973); and J. Fuhrhop and G. Benzlin, *Organic Synthesis*, Verlag Chemie (1983). Included among the nitrogen protective groups are t-butoxycarbonyl (Boc), benzoyloxycarbonyl, acetyl, allyl, phthalyl, benzyl, benzoyl, trityl and the like.

Certain compounds of this invention are preferred. Compounds of the Formula I, wherein V is W and W is $-C(-Y)-YR_5$ or $-C(-Y)-NR_4-O-R_5$, and Y is $-O-$ or $-S-$ are preferred. Thus (3S,5S,6S)-6-[(N^a-[N^a-(tert-Butoxycarbonyl)-L-phenylalanyl]-L-histidyl]amino]-2,8-dimethyl-5-hydroxy-3-[(isobutoxycarbonyl)amino]nonane;

(3S,5S,6S)-6-[(N^a-[N^a-(tert-Butoxycarbonyl)-L-phenylalanyl]-L-histidyl]amino)-2,8-dimethyl-5-hydroxy-3-[(isopropylamino)carbonyl]amino]nonane; and

(3S,5S,6S)-6-[(N^a-[N^a-(tert-Butoxycarbonyl)-L-phenylalanyl]-L-histidyl]amino)-2,8-dimethyl-5-hydroxy-3-[(methoxyamino)carbonyl]amino]nonane are preferred.

Also preferred are compounds of the formula I, wherein V is G₁₂₁-H₁₃₁-I₁₄-Z and Z is $-N(R_{10})(OR_{14})$. Thus

Boc-Phe-His-Sta-Ile-NHOCH₃, or L-Histidinamide, N-[(1-dimethyl-ethoxy)carbonyl]-L-phenylalanyl-N-[2-hydroxy-4-[(methoxyamino)carbonyl]-2-methylbutyl]amino]-1-(2-methylpropyl)-(4-oxobutyl)-, [1S-[1R*,2R*,4(1R*,2R*)]]-;

Boc-Phe-His-Sta-Ile-NHOC₂H₅, or L-Histidinamide, N-[(1,1-dimethylethoxy)carbonyl]-L-phenylalanyl-N-[4-[(1-[(ethoxyamino)carbonyl]-2-methylbutyl]amino]-2-hydroxy-1-(2-methylpropyl)-4-oxo-butyl]-, [1S-[1R*,2R*,4(1R*,2R*)]]-;

Boc-Phe-His-LVA-Ile-NHOCH₂-phenyl, or L-Histidinamide, N-[(1,1-dimethylethoxy)carbonyl]-L-phenylalanyl-N-[2-hydroxy-5-methyl-4-[(2-methyl-1-[(phenylmethoxy)amino]carbonyl]butyl]amino]carbonyl]-1-(2-methylpropyl)hexyl]-, [1S-[1R*,2R*,4R*(1R*,2R*)]]-; are preferred.

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In the Preparations and Examples below and throughout this document:

1 $^1\text{H-NMR}$ is nuclear magnetic resonance

2 Amp is 2-(aminomethyl)pyridinyl

5 Bn is benzylester

6 BOC is *t*-butoxycarbonyl

7 Bz is benzyl

8 C is centigrade

9 Cbz is benzyloxycarbonyl

10 CDCl_3 is deuteriochloroform

11 Celite is a filter aid

12 DCC is dicyclohexylcarbodiimide

13 DEPC is diethylphosphoryl cyanide

14 EtOAc is ethyl acetate

15 FTrp is *N*ⁱⁿ-formyl-Trp

16 g is grams

17 His is histidine

18 HOBt is 1-hydroxybenzotriazole

19 HPLC is high performance liquid chromatography

20 Ile is isoleucine

21 IR is infrared spectra

22 LVA is Leu ϕ (CH(OH)CH₂)Val with the S configuration at C4 (the hydroxyl-bearing carbon atom)

23 M or mol is mole

24 Me is methyl

25 min. is minute

26 ml is milliliter

27 MPLC is medium pressure liquid chromatography

28 MS is mass spectroscopy

30 Ph is phenyl

31 Phe is phenylalanine

32 RIP means a compound having the formula H-Pro-His-Phe-His-Phe-Phe-Val-Tyr-Lys-OH.₂(CH₃C(O)OH).-XH₂O which is a known renin-inhibiting peptide.

33 Sta is statine

34 TBS or TBDI7S is tert-butyldimethylsilyl

35 TEA is triethylamine

36 TFA is trifluoroacetic acid

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THF is tetrahydrofuran

TLC is thin layer chromatography

Tos is p-toluenesulfonyl

TsOH is p-toluenesulfonic acid.

5 The wedge-shape line indicates a bond which extends above the plane of the paper relative to the plane of the compound thereon.

The dotted line indicates a bond which extends below the plane of the paper relative to the plane of the compound thereon.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

10 The present invention is seen fully by the Examples below.

The following general procedures are employed for preparing the compounds of this invention.

Procedure A - Coupling of an acid to an amine with 1-hydroxybenzotriazole and dicyclohexylcarbodiimide

15 To a nitrogen (N_2) covered solution of the amine free base in methylene chloride is added in turn the acid, 1-hydroxybenzotriazole (HOBT) and dicyclohexylcarbodiimide (DCC). The mixture is stirred at room temperature and then filtered. The filtrate is concentrated in vacuo and the residue is treated with ethyl acetate and filtered again. The filtrate is washed once with aqueous sodium bicarbonate and brine, dried over magnesium sulfate and concentrated in vacuo. The residue is then chromatographed on silica gel to yield the coupled product.

20 Procedure B - Coupling of an acid to an amine using Mukaiyama conditions.

To a nitrogen covered solution of the amine free base in methylene chloride is added 1.5 equivalents of the acid followed by 2.4 equivalents of diisopropylethylamine (Hunig's Base) and 1.2 equivalents of 2-chloro-1-methylpyridinium iodide (Mukaiyama Salt).

25 The mixture is heated at reflux for 1 hr, allowed to cool and diluted to twice its volume with methylene chloride. The solution is washed with aqueous sodium bicarbonate and dilute brine, dried over magnesium sulfate and concentrated in vacuo. The residue is chromatographed over silica gel to yield the coupled product.

30 Procedure C - Boc group removal

A 5% solution of the Boc protected amine in an equal volume of methylene chloride and trifluoroacetic acid is allowed to stand at room temperature and then concentrated in vacuo. The residue is

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dissolved in methylene chloride or ethyl acetate and washed once with aqueous sodium bicarbonate and dilute aqueous sodium chloride, dried over magnesium sulfate and concentrated in vacuo. The residue is either chromatographed over silica gel or used as is in the next

5 step.

Procedure D - Coupling an acid to an amine using diethyl cyanophosphonate.

To a nitrogen covered 0.04 molar solution of the free amine in methylene chloride is added 1.25 equivalents of the acid followed by 10 1.25 equivalents of triethylamine and 1.4 equivalents of diethyl cyanophosphonate. The solution is allowed to stir at room temperature for 2-3 hours, diluted with methylene chloride and washed once with aqueous NaHCO_3 . The aqueous fraction is backwashed twice with methylene chloride. The organic fractions are combined, dried over 15 magnesium sulfate and concentrated in vacuo. The residue is then chromatographed over silica gel to yield the coupled product.

Procedure E - Coupling an acid to an amine using diethyl cyanophosphonate

To a nitrogen covered 0.04 molar solution of the acid in methylene chloride is added 1.25 equivalents of the amine followed by 20 1.25 equivalents of triethylamine and 1.4 equivalents of diethyl cyanophosphonate. The solution is allowed to stir at room temperature for 2-3 hours, diluted with methylene chloride and washed once with aqueous sodium bicarbonate. The aqueous fraction is backwashed 25 twice with methylene chloride. The organic fractions were combined, dried over magnesium sulfate and concentrated in vacuo. The residue is then chromatographed over silica gel to yield the coupled product.

Procedure F - Boc Group Removal

A 5% solution of the Boc protected amine in an equal volume of 30 methylene chloride and trifluoroacetic acid is allowed to stir at room temperature for 1 hour and then concentrated in vacuo. A solution of the residue in methylene chloride is washed once with aqueous sodium bicarbonate. The aqueous wash is backwashed twice with methylene chloride. The combined organic fractions are dried 35 over magnesium sulfate and concentrated in vacuo. The residue is then used as is in the next step without further purification.

Preparation 1 (3S,5S,6S)-3-(Benzylloxycarbonylamino)-6-(t-butoxycarbonylamino)-5-(t-butylidimethyl-silyl-

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oxy)-2,8-dimethylnonane.

To a N_2 covered ice bath cooled solution of 0.5 g (1.12 mmol) of the acid (Compound A-1, Chart A) in 7.0 ml of acetone, 0.55 ml of H_2O and 0.172 ml (1.23 mmol) of triethylamine is added 0.160 ml (1.23 mmol) of isobutylchloroformate. After stirring in the cold for 30 min there is added a solution of 0.365 g of sodium azide in 2.0 ml of H_2O over 3 min. After stirring for an additional hour in the cold, the mixture is pipetted into 15 ml of ice water. The resulting mixture is extracted 3 times with ice cold EtOAc. The combined extracts are dried over $MgSO_4$ and concentrated in vacuo. The residue is concentrated 2 additional times from benzene and allowed to stand for 18 hrs in vacuo. A solution of the residue in 5 ml of benzyl alcohol is heated to 90-95° in an oil bath for 2 hrs 50 min, allowed to cool and then concentrated in vacuo. The residue is chromatographed over silica gel using 7.5% EtOAc:hexane to yield 0.416 g (67.4%) of rearranged product. The NMR compares with material from another run, the structure of which is supported by NMR and high resolution FAB mass spec.

Found: $[m \cdot + H]^+$ at m/z 551. Theory for $C_{30}H_{55}N_2O_5Si$, 551.3880; Measured, 551.3903.

Example 1 (3S,5S,6S)-3-(Benzylxycarbonylamino)-6-[(N^2 -[N^2 -(t-butoxycarbonyl)phenylalanyl]-L-histidyl]amino)-2,8-dimethyl-5-hydroxynonane.

Part A.

By the general procedure C for Boc group removal, 0.209 g (0.379 mmol) of the Boc amino urethane (Preparation 1) yields 0.204 g of the crude free amine. The amine is then coupled (procedure B) with Boc(tosyl)histidine. The chromatography is carried out using 1.8% MEOH:CH₂Cl₂ containing 0.18% of NH₄OH to yield 0.254 g (79.6%) of coupled product. The structure is supported by NMR and high resolution FAB mass spec.

Found: $[m \cdot + H]^+$ at m/z 842; Theory for $C_{43}H_{68}N_5O_8SSi$, 842.4558; Measured, 842.4544.

Part B.

By the general procedure C for Boc group removal, 0.254 g (0.302 mmol) of Boc peptide from Part A yields 0.201 g of crude free amine. The amine is then coupled (procedure B) with Boc phenylalanine and chromatographed with 3% MEOH:CH₂Cl₂ containing 0.3% NH₄OH to yield

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0.241 g of coupled product contaminated with 1-methyl-2-pyridone. The structure is supported by NMR and high resolution FAB mass spec.

Found: $[m \cdot + H]^+$ at m/z 875; Theory for $C_{46}H_{63}N_6O_9S$, 875.4377; Measured, 875.4354.

5 Part C.

To a N_2 covered solution of 0.233 g of the tosyl protected peptide mixture from the previous reaction (Part B) in 2.6 ml of DMF and 13 ml of THF is added 0.36 (2.66 mmol) of 1-hydroxybenzotriazole. After stirring at room temperature for 25 hrs the mixture is 10 concentrated in vacuo. The residue is chromatographed over silica gel using 5% CH_2Cl_2 containing 0.5% NH_4OH to yield 0.147 of the above named peptide. The structure is supported by high resolution FAB mass spec.

Found: $[m \cdot + H]^+$ at m/z 721; Theory for $C_{39}H_{57}N_6O_7$, 721.4288; 15 Measured, 721.4273.

Example 2 (3S,5S,6S)-3-Amino-6-[(N^a [N^a -(*t*-butoxycarbonyl)-L-phenylalanyl]-L-histidyl]amino]-2,8-dimethyl-5-hydroxy-9-nonane.

A mixture of 0.096 g (0.133 mmol) of the CBZ peptide (Example 1) 20 and 0.05 g of 10% Pd/C catalyst in 10 ml of EtOH is stirred under H_2 at atmospheric pressure for 2 hrs 15 min. An additional 0.05 g of 10% Pd/C catalyst is added and stirring is continued for an additional 18 hrs. The catalyst is removed by filtration and the filtrate concentrated in vacuo. The residue is chromatographed over silica 25 gel using 30% CH_2Cl_2 containing 0.5% NH_4OH to yield 0.062 g (79.4%) of the title compound. The structure is supported by high resolution FAB mass spec.

Found: $[m \cdot + H]^+$ at m/z 587; Theory for $C_{31}H_{51}N_6O_5$, 587.3921; Measured, 587.3896.

30 Example 3 (3S,5S,6S)-6-[(N^a [N^a -(*t*-Butoxycarbonyl)-L-phenyl-alanyl]-L-histidyl]amino]-2,8-dimethyl-5-hydroxy-3-[(isopropoxycarbonyl)amino]nonane.

Part A.

A mixture of 0.203 g (0.369 mmol) of CBZ peptide (Preparation 1) 35 and 0.10 g of 10% Pd/C catalyst in 10 ml of EtOH is stirred under H_2 at atmospheric pressure for 2 hrs 45 min. The catalyst is removed by filtration and the filtrate is concentrated in vacuo to yield 0.146 g (94.9%) of free amine. The structure is supported by NMR and high

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resolution FAB mass spec.

Found: $[m \cdot + H]^+$ at m/z 417; Theory for $C_{22}H_{49}N_2O_3Si$, 417.3512;
Measured, 417.3531.

Part B.

5 To a N_2 covered, ice bath cooled solution of 0.092 g (0.221 mmol) of the free amine (Part A) and 0.077 ml of triethylamine in 4 ml of THF is added 0.055 ml of isopropylchloroformate. The ice bath is allowed to melt and the mixture is then stirred at room temperature for 16 hrs. The reaction mixture is then pipetted into 10 10 ml of ice water and then extracted three times with CH_2Cl_2 . The combined extracts are dried over $MgSO_4$ and concentrated in vacuo. The residue is chromatographed over silica gel using 10% EtOAc:hexane to yield 0.091 g (81.9%) of the urethane. The structure is supported by NMR and high resolution FAB mass spec.

15 Found: $[m \cdot + H]^+$ at m/z 503; Theory for $C_{26}H_{55}N_2O_5Si$, 503.3880;
Measured, 503.3907.

Part C.

By the general procedure C for Boc group removal, 0.086 g (0.171 mmol) of the Boc peptide (Part B) yields 0.091 g of the crude amine. 20 The amine is then coupled with Boc(Tosyl)-histidine (procedure B) and chromatographed using 2% MeOH: CH_2Cl_2 containing 0.2% NH_4OH to yield 0.116 g (85.4%) of the coupled peptide. The structure is supported by NMR and high resolution FAB mass spec.

25 Found: $[m \cdot + H]^+$ at m/z 794; Theory for $C_{39}H_{68}N_5O_8SSi$.
794.4558; Measured, 794.4565.

Part D.

According to the general procedure C for Boc group removal, 0.113 g (0.142 mmol) of the Boc amine (Part C) yields 0.087 g of crude free amine. This amine is then coupled (procedure B) with Boc 30 phenylalanine and chromatographed using 3% MeOH: CH_2Cl_2 containing 0.3% NH_4OH to yield 0.115 g of coupled peptide contaminated with 1-methyl-2-pyridone. The structure is supported by NMR and high resolution FAB mass spec.

35 Found: $[m \cdot + H]^+$ at m/z 827; Theory for $C_{42}H_{63}N_6O_4S$.
827.4377; Measured, 827.4383.

Part E.

To a N_2 covered solution of 0.113 g of the tosyl protected peptide mixture from the previous reaction (Part D) in 1.3 ml of DMF

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and 7.0 ml of THF is added 0.18 g (1.37 mmol) of 1-hydroxybenzotriazole. After stirring at room temperature for 22 hrs the solution is concentrated in vacuo. The residue is chromatographed over silica gel using 5% MEOH:CH₂Cl₂ containing 0.5% NH₄OH to yield 0.061 g of 5 titled product. The structure is supported by NMR and high resolution mass spec.

Found: [m[•] + H]⁺ at m/z 673; Theory for C₃₅H₅₇N₆O₇, 673.4288; Measured, 673.4293.

Example 4 10 (3S,5S,6S)-6-[(N²[N²-(t-Butoxycarbonyl)-L-phenyl-alanyl-L-histidyl]amino)-2,8-dimethyl-5-hydroxy-3-[(3-methyl-1-oxobutyl)amino]nonane.

Part A.

By coupling procedure A, 0.20 g (0.48 mmol) of the amine (Example 3, part A) is coupled with isovaleric acid using 1.5 equivalents of the acid, HOBT and DCC. After a reaction time of 2.25 hrs, an additional 1.5 equivalents of the acid, HOBT and DCC are added and the reaction is continued for 17 hrs. At this time, 5 ml of DMF is added and stirring is continued for an additional 1 hr 40 min. The reaction is then worked up according to the standard procedure and chromatographed over silica gel using 10% EtOAc:hexane to yield 0.248 g (103%) of coupled product containing some unknown extraneous material. The structure is supported by NMR and high resolution FAB mass spec.

Found: [m[•] + H]⁺ at m/z 501; Theory for C₂₇H₅₇N₂O₄Si, 501.4087; Measured, 501.4051.

Part B.

Using the general procedure C for Boc group removal, 0.248 g of the material from the previous reaction (Part A) yields 0.160 g of crude free amine. The amine is then coupled (procedure B) with 30 Boc(tosyl)histidine and chromatographed using 1.8% MEOH:CH₂Cl₂ containing 0.18% NH₄OH to yield 0.252 g of coupled product. The structure is supported by NMR and high resolution FAB mass spec.

Found: [m[•] + H]⁺ at m/z 792; Theory for C₄₀H₇₀N₅O₇SSI, 792.4765; Measured, 792.4739.

35 Part C.

By the general procedure C for Boc group removal, 0.252 g (0.318 mmol) of the Boc peptide (Part B) yields 0.203 g of the crude free amine. The amine is then coupled (procedure B) with Boc phenyl-

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alanine and chromatographed using 3% MeOH:CH₂Cl₂ containing 0.3% NH₄OH to yield 0.187 g (71.3%) of the coupled product. The structure is supported by NMR and high resolution FAB mass spec.

Found: [m[·] + H]⁺ at m/z 825; Theory for C₄₃H₆₅N₆O₈S, 825.4584;
5 Measured, 825.4590.

Part D.

To a N₂ covered solution of 0.187 (0.227 mmol) of the tosyl protected peptide (Part C) in 2.2 ml of DMF and 11.5 ml of THF is added 0.31 g (2.27 mmol) of 1-hydroxybenzotriazole. After stirring 10 at room temperature for 22 hrs the solution is concentrated in vacuo. The residue is chromatographed over silica gel using 6.25% MeOH:CH₂Cl₂ containing 0.5% NH₄OH to give 0.119 g (78.1%) of the titled product. The structure is supported by NMR and high resolution FAB mass spec.

15 Found: [m[·] + H]⁺ at m/z 671; Theory for C₃₆H₅₉N₆O₆, 671.4496;
Measured, 671.4501.

Example 5 (3S,5S,6S)-3-[(N^α-[N^α-(Benzylloxycarbonyl)-D-valyl])-amino]-6-[(N^α-[N^α-(t-butoxycarbonyl)-L-phenylalanyl]-L-histidyl)amino]-2,8-dimethyl-5-hydroxynonane.

20 Part A.

Using coupling procedure B, 0.10 g (0.24 mmol) of the amine (Example 3, Part A) is coupled with CBZ-D-valine and chromatographed with 15% EtOAc:hexane to yield 0.131 g (84.0%) of the coupled product. The structure is supported by NMR and high resolution FAB 25 mass spec.

Found: [m[·] + H]⁺ at m/z 650; Theory for C₃₅H₆₅N₃O₆Si, 650.45646; Measured, 650.4540.

Part B.

According to the general procedure C for Boc group removal, 30 0.291 g (0.448 mmol) of the Boc peptide (Part A) yields 0.287 g of the crude free amine. The amine is then coupled (procedure B) to Boc(tosyl)histidine and chromatographed using 1.8% MeOH:CH₂Cl₂ containing 0.18% NH₄OH to yield 0.349 g (81.1%) of coupled product. The structure is supported by NMR and high resolution FAB mass spec.

35 Found: [m[·] + H]⁺ at m/z 941; Theory for C₄₈H₇₇N₆O₉SSi, 941.52426; Measured, 941.5212.

Part C.

By the general procedure C for BOC group removal, 0.342 g (0.363

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mmol) of the Boc peptide (Part B) yields 0.306 g of the crude free amine. The amine is then coupled (procedure B) to Boc phenylalanine and chromatographed using 3.5% MeOH:CH₂Cl₂ containing 0.35% NH₄OH to yield 0.343 g of crystalline material (m.p. 183-191°) contaminated 5 with 1-methyl-2-pyridone. The structure is supported by NMR and high resolution FAB mass spec.

Found: [m· + H]⁺ at m/z 974. Theory for C₅₁H₇₂N₇O₁₀, 974.5061; Measured, 974.5030.

Part D.

10 To a N₂ covered solution of 0.341 g of the tosyl protected mixture from the previous reaction (Part C) in 3.4 ml of DMF and 17 ml of THF is added 0.47 g (3.5 mmol) of 1-hydroxybenzotriazole. After stirring for 16 hr the solution is concentrated in vacuo. The residue is chromatographed over silica gel using 5% MeOH:CH₂Cl₂ 15 containing 0.5% NH₄OH to yield 0.253 g of titled product. The structure is supported by NMR and high resolution FAB mass spec.

Found: [m· + H]⁺ at m/z 820. Theory for C₄₄H₆₆N₇O₈, 820.4973; Measured, 820.4950.

Example 6 (3S,5S,6S)-6-[(N²-(t-butoxycarbonyl)-L-phenyl-alanyl)-L-histidyl]amino]-2,8-dimethyl-5-hydroxy-3-[(D-valyl)amino]nonane.

20 A mixture of 0.137 g (0.167 mmol) of the CBZ amine (Example 5) and 0.06 g of 10% Pd/C catalyst in 10 ml of EtOH is stirred under H₂ at atmospheric pressure for 35 min. An additional 0.06 g of catalyst is added and stirring is continued for 19 hr. The catalyst is removed by filtration and the filtrate is concentrated in vacuo. The residue is chromatographed over silica gel with 6% MeOH:CH₂Cl₂ 25 containing 0.5% NH₄OH to yield 0.094 (82.1%) of titled product. The structure is supported by NMR and high resolution FAB mass spec.

30 Found: [m· + H]⁺ at m/z 686. Theory for C₃₆H₆₀N₇O₆, 686.4605; Measured, 686.4601.

Example 7 (3S,5S,6S)-3-[(N²-(3-aminomethyl)benzoyl)-D-valyl]-amino]-6-[(N²-(t-butoxycarbonyl)-L-phenylalanyl)-L-histidyl]amino]-2,8-dimethyl-5-hydroxynonane.

35 Part A.

A mixture of 0.131 g (0.202 mmol) of CBZ amine (Example 5, Part A) and 0.05 g of 10% Pd/C catalyst in 10 ml of EtOH is stirred under H₂ at atmospheric pressure for 1.2 hr. The catalyst is removed by

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filtration and the filtrate concentrated in vacuo to yield 0.101 g (96.9%) of free amine. The structure is supported by NMR.

Part B.

By coupling procedure B, 0.101 g (0.196 mmol) of the free amine (Part A) is coupled with 3-cyanobenzoic acid and chromatographed with 1.25% MeOH:CH₂Cl₂ containing 0.125% NH₄OH to yield 0.112 g (88.6%) of coupled product. The structure is supported by NMR and high resolution FAB mass spec.

Found: [m[·] + H]⁺ at m/z 645. Theory for C₃₅H₆₁N₄O₅Si, 10 645.4411; Measured, 645.4382.

Part C.

By the general procedure C for Boc group removal, 0.112 g (0.174 mmol) of the Boc peptide (Part B) yields 0.090 g of the free amine. The amine is then coupled (coupling procedure B) with Boc(tosyl)histidine and chromatographed with 1.75% MeOH:CH₂Cl₂ containing 15 0.175% NH₄OH to yield 0.134 g (82.3%) of coupled product. The structure is supported by NMR and high resolution FAB mass spec.

Found: [m[·] + H]⁺ at m/z 936. Theory for C₄₈H₇₄N₇O₈SSI, 20 936.5089; Measured, 936.5063.

Part D.

By the general procedure C for Boc group removal, 0.129 g (0.138 mmol) of the Boc peptide (Part C) yields 0.110 g of the free amine. The amine is then coupled (coupling procedure B) with Boc phenylalanine and chromatographed with 3.5% MeOH:CH₂Cl₂ containing 25 0.35% NH₄OH to yield 0.124 g of coupled product mixed with 1-methyl-2-pyridone. The structure is supported by NMR and high resolution FAB mass spec.

Found: [m[·] + H]⁺ at m/z 969. Theory for C₅₁H₆₉N₈O₉S, 30 969.4908; Measured, 969.4945.

Part E.

To a N₂ covered solution of 0.124 g of the peptide mixture from the previous reaction (Part D) in 1.2 ml of DMF and 6.5 ml of THF is added 0.17 g of 1-hydroxybenzotriazole. After stirring at room temperature for 19 hr the solution is concentrated in vacuo. The 35 residue is chromatographed over silica gel using 6.25% MeOH:CH₂Cl₂ containing 0.5% NH₄OH to yield 0.077 g of product. The structure is supported by high resolution FAB mass spec.

Found: [m[·] + H]⁺ at m/z 815. Theory for C₄₄H₆₂N₈O₇, 815.4819;

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.35.

Measured, 815.4848.

Part F.

A mixture of 0.077 g (0.095 mmol) of the cyano peptide, (Part E) 0.076 ml of 1.6 N HCl in Et₂O and 0.05 g of 5% Pd/C catalyst in 150 ml of EtOH is placed on a pressure hydrogenator for 18 hr. The catalyst is removed by filtration and the filtrate is concentrated in vacuo. The residue is treated with CH₂Cl₂ and a small amount of aqueous NaHCO₃ and mixed well. The aqueous fraction along with some solid material is separated and extracted with EtOAc. The solid material is then removed by filtration, washed once with a couple of drops of H₂O and dried in vacuo to yield crude product A. The organic layers are combined, dried over MgSO₄ and concentrated in vacuo to yield crude product B. Crude products A & B are combined and chromatographed over silica gel using 10% MeOH:CH₂Cl₂ containing 0.5% NH₄OH to yield first 0.028 g of recovered starting cyano peptide followed by 0.024 g (31.0%) of titled product.

Example 8 (3S,5S,6S)-6-[[N²-(t-Butoxycarbonyl)-L-phenyl-alanyl]-L-histidyl]amino]-2,8-dimethyl-5-hydroxy-3-[(N²-[(2-pyridinyl)ethanoyl]-D-valyl]amino]nonane.

20 Part A.

To a N₂ covered partial solution of 0.06 g (0.340 mmol) of 2-pyridylacetic acid hydrochloride in 20 ml CH₂Cl₂ is added 0.16 ml (0.907 mmol) of diisopropylethylamine. After stirring at room temperature for 5 min there is added a solution 0.117 g (0.227 mmol) of the amine (Example 7, Part A) in 6 ml of CH₂Cl₂ followed by 0.07 g (0.272 mmol) of 2-chloro-1-methylpyridinium iodide. The mixture is heated at reflux in an oil bath at 50° and then allowed to cool and stand at room temperature for 1 hr. The mixture is then diluted with 20 ml of CH₂Cl₂, washed once with aqueous NaHCO₃ and brine, dried over MgSO₄ and concentrated in vacuo. The residue is chromatographed over silica gel using 3%MeOH:CH₂Cl₂ containing 0.3% NH₄OH to yield 0.153 g of product contaminated with 1-methyl-2-pyridone. The structure is supported by NMR and high resolution FAB mass spec.

Found: [m. + H]⁺ at m/z 635. Theory for C₃₄H₆₃N₄O₅Si, 35 635.4567; Measured, 635.4602.

Part B.

By the general procedure C for Boc group removal, 0.151 g (0.238 mmol) of protected peptide (Part A) yields 0.136 g of the crude free

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amine. The amine is then coupled (procedure B) with Boc(tosyl)-histidine and chromatographed with 3% MeOH:CH₂Cl₂ containing 0.3% NH₄OH to yield 0.193 g of coupled peptide contaminated with 1-methyl-2-pyridone. The structure is supported by NMR and high resolution FAB mass spec.

5 Found: [m· + H]⁺ at m/z 926. Theory for C₄₇H₇₆N₇O₈SSi, 926.5245; Measured, 926.5263.

Part C.

According to the general procedure C for Boc group removal, 10 0.193 g of the protected peptide mixture from the previous reaction (Part B) yields 0.148 g of the crude free amine. The amine is then coupled (procedure B) with Boc phenylalanine and chromatographed with 4% MeOH:CH₂Cl₂ containing 4% NH₄OH to yield 0.096 g of the coupled peptide. The structure is supported by NMR and high resolution FAB 15 mass spec.

Found: [m· + H]⁺ at m/z 959. Theory for C₅₀H₇₁N₈O₉S, 959.5064; Measured, 959.5059.

Part D.

To a solution of 0.089 g (0.0928 mmol) of the tosyl protected 20 peptide (Part C) in 0.9 ml of DMF and 5.0 ml of THF is added 0.13 g of 1-hydroxybenzotriazole. After stirring for 21 hrs the solution is concentrated in vacuo. The residue chromatographed over silica gel using 7% MeOH:CH₂Cl₂ containing 0.5% NH₄OH to yield 0.066 g (88.3%) of titled product. The structure is supported by high resolution FAB 25 mass spec.

Found: [m· + H]⁺ at m/z 805. Theory for C₄₃H₆₅N₈O₇, 805.4976; Measured, 805.4983.

Example 9 (3S,5S,6S)-6-[(N^α-[N^α-(tert-Butoxycarbonyl)-L-phenyl-alanyl]-L-histidyl]amino]-2,8-dimethyl-5-hydroxy-3-30 [(isobutoxycarbonyl)amino]nonane.

Part A.

To a nitrogen covered ice-bath cooled solution of 0.20 g (0.480 mmol of the amine of Example 3 (Part A) and 0.17 ml (1.20 mmol) of triethylamine in 9 ml of THF is added 0.16 ml (1.20 mmol) of isobutylchloroformate. The ice is allowed to melt and the reaction 35 mixture is warmed and is allowed to stir at room temperature. After 22.5 hours the reaction is poured into ice water and extracted three times with methylene chloride. The combined extracts are washed with

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dilute brine, dried over magnesium sulfate and concentrated in vacuo. The residue is chromatographed on a 200 ml silica gel column (elution with 10% ethyl acetate:hexane), 4.8 ml fractions are collected. Fractions 86-140 were combined to yield 0.218 g (87.9%) of the 5 urethane. The structure is supported by NMR and high resolution FAB mass spec.

Found: $[\text{m}^+\text{H}]^+$ at m/z 517. Theory for $\text{C}_{27}\text{H}_{57}\text{N}_2\text{O}_5\text{Si}$; 517.4036; Measured, 517.4031.

Part B.

10 By the general procedure F for Boc group removal 0.218 g (0.421 mmol) of the Boc peptide (Part A) yields 0.164 g of the free amine. The amine is then coupled (coupling procedure D) with Boc-im-tosyl-histidine and chromatographed using 1.25% MeOH:methylene chloride containing 0.125% NH_4OH to yield 0.293 g (86.1%) of coupled product.

15 The structure is supported by NMR and high resolution FAB mass spec.

Found: $[\text{m}^+\text{H}]^+$ at m/z 808; Theory for $\text{C}_{40}\text{H}_{70}\text{N}_5\text{O}_8\text{SSi}$, 808.4714; Measured, 808.4722.

Part C.

20 By the general procedure F for Boc group removal 0.10 g (0.124 mmol) of the Boc peptide (Part B) yields 0.084 g of the free amine. The amine is then coupled (coupling procedure D) with Boc phenylalanine and chromatographed using 3% MeOH:methylene chloride containing 0.3% NH_4OH to yield 0.096 g (92.0%) of coupled product. The structure is supported by NMR and high resolution FAB mass spec.

25 Found: $[\text{M}^+\text{H}]^+$ at m/z 841; theory for $\text{C}_{43}\text{H}_{65}\text{N}_6\text{O}_9\text{S}$, 841.4533; Measured, 841.4528.

Part D.

30 To a nitrogen covered solution of 0.096 g (0.114 mmol) of the tosyl peptide (Part C) in 1.1 ml of DMF and 5.9 ml of THF is added 0.16 g (1.16 mmol) of 1-hydroxybenzotriazole. The solution is stirred at room temperature for 22 hours and then concentrated in vacuo. The residue is chromatographed over silica gel using 4% MeOH:CH₂Cl₂ containing 0.4% NH_4OH to yield 0.059 g (75.3%) of titled product. The structure is supported by high resolution FAB mass spec.

35 Found: $[\text{m}^+\text{H}]^+$ at m/z 687; theory for $\text{C}_{36}\text{H}_{59}\text{N}_6\text{O}_7$, 687.4445; Measured, 687.4402.

Example 10 (3S,5S,6S)-6-[[N²-[N²-(tert-Butoxycarbonyl)-L-phenyl-

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alanyl]-L-histidyl]amino]-2,8-dimethyl-5-hydroxy-3-
[(isopropylamino)carbonyl]amino]nonane.

Part A.

A N_2 covered solution of 0.10 g (0.240 mmol) of the amine of
5 Example 3 (Part A) and 0.026 ml (0.264 mmol) of isopropylisocyanate
in 2 ml of THF is heated at 55° for 2 hr and then concentrated in
vacuo. The latter residue and 0.062 g of a residue from a previous
0.120 mmol run are combined and chromatographed on a 150 ml silica
10 gel column (elution with 1% MeOH:CH₂Cl₂) and 5.0 ml fractions are
collected. Fractions 131-168 are combined to yield 0.162 g (89.7%)
of the urea. The structure is supported by NMR and mass spec.

Part B.

By the general procedure F for Boc group removal 0.164 g (0.327
mmol) of the Boc peptide (Part A) yields 0.148 g of the free amine.
15 The amine is then coupled (coupling procedure D) with Boc-im-tosyl-
histidine and chromatographed using 1.5% MeOH:CH₂Cl₂ containing 0.15%
NH₄OH to yield 0.239 g of coupled product. The structure is
supported by NMR and FAB mass spec.

Found: [m[•] + H]⁺ at m/z 793.

20 Part C.

By the general procedure F for Boc group removal 0.10 g (0.126
mmol) of the Boc peptide (Part B) yields 0.08 g of the free amine.
The amine is then coupled (coupling procedure D) with Boc phenyl-
alanine and chromatographed using 3.75% MeOH:CH₂Cl₂ containing 0.375%
25 NH₄OH to yield 0.059 g (56.7%) of coupled product. The structure is
supported by NMR and FAB mass spec.

Found: [m[•] + H]⁺ at m/z 826.

Part D.

To a N_2 solution of 0.059 g (0.0714 mmol) of the tosyl peptide
30 (Part C) in 0.7 ml of DMF and 3.6 ml of THF is added 0.097 g (0.714
mmol) of 1-hydroxybenzotriazole. The solution is stirred at room
temperature for 18.5 hrs and then concentrated in vacuo. The residue
is chromatographed over silica gel using 6.25% MeOH:CH₂Cl₂ containing
0.5% NH₄OH to yield 0.044 g (91.7%) of titled product. The structure
35 is supported by NMR and high resolution FAB mass spec.

Found: [m[•] + H]⁺ at m/z 672; theory for C₃₅H₅₈N₇O₆, 672.4448;
Measured, 672.4431.

Example 11 (3S,5S,6S)-6-[(N²-[N²-(tert-Butoxycarbonyl)-L-phenyl-

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alanyl]-L-histidyl]amino]-2,8-dimethyl-5-hydroxy-3-[(methoxyamino)carbonyl]amino]nonane.

Part A.

To a N_2 covered ice bath cooled solution of 0.2 g (0.449 mmol) of the acid (Compound A-1, Chart A) and 0.07 ml (7.493 mmol) of triethylamine in 2.8 ml of acetone and 0.22 ml of water is added 0.064 ml (0.493 mmol) of isobutylchloroformate. After stirring in the cold for 40 min there is added a solution of 0.15 g of sodium azide in 0.8 ml of water over 1.5 min. The mixture is then stirred in the cold for 2 hr 20 min, mixed with 10 ml of ice water and extracted three times with cold EtOAc. The combined extracts are washed once with cold brine, dried over $MgSO_4$ and concentrated in vacuo. The residue is concentrated two additional times from toluene. A solution of the residue in 2 ml of THF is added to a mixture of 0.11 g (1.35 mmol) of methoxyamine hydrochloride and 0.19 ml (1.35 mmol) of triethylamine in 4 ml of THF. (This mixture had been stirring for 24 hrs prior to the addition). The resulting mixture is stirred at 55° for 2.5 hrs, at room temperature for 16 hrs and then concentrated in vacuo. A solution of the residue in CH_2Cl_2 is washed once with water and dilute brine, dried over $MgSO_4$ and concentrated in vacuo. The residue is chromatographed on a 150 ml silica gel column (eluting with 1% MeOH: CH_2Cl_2) and 5.1 ml fractions are collected. Fractions 131-176 are combined to yield 0.156 g (70.9%) of the urea. The product is compared (NMR, TLC) with material prepared from a previous run, the structure of which is supported by NMR and high resolution FAB mass spec.

Found: $[m \cdot + H]^+$ at m/z 490; theory for $C_{24}H_{52}N_3O_5Si$, 490.3676; Measured, 490.3688.

Part B.

By the general procedure F for Boc group removal 0.219 g (0.447 mmol) of the Boc peptide (Part A) yielded 0.176 g of the free amine. The amine is then coupled (coupling procedure D) with Boc-im-tosyl-histidine and chromatographed using 2% MeOH: CH_2Cl_2 containing 0.2% NH_4OH to yield 0.294 g (84.2%) of coupled product. The structure is supported by NMR and FAB mass spec.

Found: $[m \cdot + H]^+$ at m/z 781.

Part C.

By the general procedure F for Boc group removal 0.10 g (0.128

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mmol) of the Boc peptide (Part B) yields 0.099 g of the free amine. The amine is then coupled (coupling procedure D) with Boc-phenylalanine and chromatographed using 4% MeOH:CH₂Cl₂ containing 0.4% NH₄OH to yield 0.079 g (75.8%) of coupled product. The structure is supported by NMR and FAB mass spec.

5 Found: [m· + H]⁺ at m/z 814.

Part D.

To a N₂ covered solution of 0.079 g (0.0971 mmol) of the tosyl peptide (Part C) in 1.0 ml of DMF and 5.0 ml of THF is added 0.13 g (0.962 mmol) of 1-hydroxybenzotriazole. The solution was stirred at room temperature for 24 hrs and then concentrated in vacuo. The residue is chromatographed over silica gel using 7.0% MeOH:CH₂Cl₂ containing 0.5% NH₄OH to yield 0.058 g (90.5%) of titled product. The structure is supported by NMR and high resolution FAB mass spec.

10 Found: [m· + H]⁺ at m/z 660; theory for C₃₄H₅₄N₇O₇, 660.4084; Measured, 660.4080.

Example 12 (3S,5S,6S)-6-[[N²-[N²-(tert-Butoxycarbonyl)-L-phenylalanyl]-L-histidyl]amino]-2,8-dimethyl-5-hydroxy-3-[(propylamino)thiocarbonyl]amino]nonane.

15 Part A.

A N₂ covered solution of 0.10 g (0.240 mmol) of the amine of Example 3 (Part A) and 0.027 g (0.264 mmol) of propylisothiocyanate in 2 ml of dioxane is stirred at 55° for 2 hr, at 75° for 2.25 hr and then allowed to stand at room temperature for 3 days. The reaction 20 mixture is concentrated in vacuo and the residue is chromatographed over a 100 ml silica gel column (elution with 10% EtOAc:hexane) and 5.2 ml fractions are collected. Fractions 60-102 are combined to yield 0.089 g (71.6%) of the thiourea. The structure is supported by NMR and FAB mass spec.

25 Found: [m· + H]⁺ at m/z 517.

Part B.

30 By the general procedure F for Boc group removal 0.089 g (0.172 mmol) of the Boc peptide (Part A) yields 0.071 g of the free amine. The amine is then coupled (coupling procedure D) with Boc-im-tosyl-histidine and chromatographed using 1% MeOH:CH₂Cl₂ containing 0.1% NH₄OH to yield 0.121 g (86.9%) of coupled product. The structure is supported by NMR and FAB mass spec.

35 Found: [m· + H]⁺ at m/z 809.

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Part C.

By the general procedure F for Boc group removal, 0.121 g (0.150 mmol) of the Boc peptide (Part B) yields 0.100 g of product as a two part mixture. This material is then coupled (coupling procedure D) 5 with Boc phenylalanine and chromatographed over a 150 ml silica gel column (elution with 0.67% MeOH:CH₂Cl₂ containing 0.67% NH₄OH to fraction 192, then 1.25% MeOH:CH₂Cl₂ containing 0.125% NH₄OH to fraction 340, then 3% MeOH:CH₂Cl₂ containing 0.3% NH₄OH). There are collected 5.3 ml fractions to fraction 340 and then two 500 ml 10 fractions are collected. Fractions 160-230 are combined to yield 0.043 g (30.0%) of coupled product A which still retained the tert-butyldimethylsilyl (TBD17S) protecting group. The structure is supported by NMR and FAB mass spec.

Found: [m[·] + H]⁺ at m/z 956.

15 The first of the two 500 ml fractions yields 0.051 g of the coupled product B which lacked the tert-butyldimethylsilyl protecting group. The structure is supported by NMR and FAB mass spec.

Found: [m[·] + H]⁺ at m/z 842.

Part D.

20 To a N₂ covered solution of 0.051 g (0.0606 mmol) of the tosyl peptide (Product B, Part C) in 0.6 ml of DMF and 3.0 ml of THF is added 0.082 g (0.606 mmol) of 1-hydroxybenzotriazole. The solution is stirred at room temperature for 17.5 hrs and then concentrated in vacuo. The residue is chromatographed over silica gel using 4% 25 MeOH:CH₂Cl₂ containing 0.4% NH₄OH to yield 0.025 g (60.0%) of titled product. The structure is supported by high resolution FAB mass spec.

Found: [m[·] + H]⁺ at m/z 688; theory for C₃₅H₅₈N₇O₅S, 688.4220; Measured, 688.4210.

30 Example 13 (3S,5S,6S)-6-[(N²-[N²-(tert-Butoxycarbonyl)-L-phenyl-alanyl]-L-histidyl]amino)-2,8-dimethyl-3-[(N,N-dimethylsulfamoyl)amino]-5-hydroxynonane.

Part A.

A N₂ covered solution of 0.226 g (0.542 mmol) of the amine of 35 Example 3 (Part A) and 0.029 ml (0.271 mmol) of dimethylsulfamoyl chloride in 5 ml of THF is heated at 70° for 46 hrs and then allowed to cool and concentrated in vacuo. The residue is chromatographed over a 150 ml silica gel column (elution with 1% MeOH:CH₂Cl₂) and 5.3

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ml fractions are collected. Fractions 127-152 are combined to yield 0.088 g (62%) of the sulfonamide. The structure of product from a previous run is supported by NMR and FAB mass spec.

Found: $[m \cdot + H]^+$ at m/z 524.

5 Part B.

By the general procedure F for Boc group removal 0.134 g (0.256 mmol) of the Boc peptide (Part A) yielded 0.106 g of the free amine. The amine is then coupled (coupling procedure D) with Boc-im-tosyl-histidine and chromatographed using 1 $\frac{1}{2}$ MeOH:CH₂Cl₂ containing 0.1% NH₄OH to yield 0.160 g (76.7%) of coupled product. The structure is supported by NMR and FAB mass spec.

10 Found: $[m \cdot + H]^+$ at m/z 815.

Part C.

By the general procedure F for Boc group removal 0.160 g (0.196 mmol) of the Boc peptide (Part B) yields 0.140 g of the free amine. The amine is then coupled (coupling procedure D) with Boc phenylalanine and chromatographed using 2.5% MeOH:CH₂Cl₂ containing 0.25% NH₄OH to yield 0.130 g (78.2%) of coupled product. The structure is supported by NMR and FAB mass spec.

15 Found: $[m \cdot + H]^+$ at m/z 848.

Part D.

To a N₂ covered solution of 0.130 g (0.153 mmol) of the tosyl peptide (Part C) in 1.6 ml of DMF and 7.9 ml of THF is added 0.21 g (0.153 mmol) of 1-hydroxybenzotriazole. The solution is stirred at room temperature for 25 hrs and then concentrated in vacuo. The residue is chromatographed over a 150 ml silica gel column using 4% MeOH:CH₂Cl₂ containing 0.4% NH₄OH to fraction 174 and then switching to 5% MeOH:CH₂Cl₂ containing 0.5% NH₄OH (fraction volumes were 5.3 ml) to yield 0.087 g (81.9%) of titled product. The structure is supported by NMR and high resolution FAB mass spec.

20 Found: $[m \cdot + H]^+$ at m/z 694; theory for C₃₃H₅₆N₇O₇S, 694.3962; Measured, 694.3971.

Example 14 (3S,5S,6S)-6-[(N²-[N²-(tert-Butoxycarbonyl)-L-phenylalanyl]-L-histidyl)amino]-3-[(ethanesulfonyl)amino]-35 2,8-dimethyl-5-hydroxynonane.

Part A.

A N₂ covered ice bath cooled solution of 0.1 g (0.240 mmol) of the amine of Example 3 (Part A) and 0.037 ml (0.264 mmol) of tri-

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ethylamine in 2 ml of CH_2Cl_2 is added 0.025 ml (0.264 mmol) of ethane sulfonyl chloride. The cold bath is removed and the mixture is stirred at room temperature for 46.5 hrs. The reaction mixture is then diluted with CH_2Cl_2 washed once with aqueous NaHCO_3 , dried over 5 MgSO_4 and concentrated in vacuo. The residue is chromatographed over a 50 ml silica gel column. (elution with 0.75% $\text{MeOH}:\text{CH}_2\text{Cl}_2$) and 4.8 ml fractions are collected. Fractions 60-86 are combined to yield 0.098 g (80.2%) of the sulfonamide. The structure of the product prepared from another run is supported by NMR and FAB mass spec.

10 Found: $[\text{m}^\cdot + \text{H}]^+$ at m/z 509.

Part B.

By the general procedure F for Boc group removal 0.078 g (0.153 mmol) of the Boc peptide (Part A) yields 0.059 g of the free amine. The amine is then coupled (coupling procedure D) with Boc-im-tosyl-15 histidine and chromatographed using 1% $\text{MeOH}:\text{CH}_2\text{Cl}_2$ containing 0.1% NH_4OH to yield 0.097 g (79.2%) of coupled product. The structure is supported by NMR and FAB mass spec.

Found: $[\text{m}^\cdot + \text{H}]^+$ at m/z 800.

Part C.

20 By the general procedure F for Boc group removal 0.117 g (0.146 mmol) of the Boc peptide (Part B) yields 0.101 g of the free amine. The amine is then coupled (coupling procedure D) with Boc phenylalanine and chromatographed using 2.5% $\text{MeOH}:\text{CH}_2\text{Cl}_2$ containing 0.25% NH_4OH to yield 0.112 g (92.1%) of coupled product. The structure is 25 supported by NMR and FAB mass spec.

Found: $[\text{m}^\cdot + \text{H}]^+$ at m/z 833.

Part D.

To a N_2 covered solution of 0.112 g (0.134 mmol) of the tosyl peptide (Part C) in 1.4 ml of DMF and 6.9 ml of THF is added 0.18 g (1.34 mmol) of 1-hydroxybenzotriazole. The solution is stirred at room temperature for 22 hrs and then concentrated in vacuo. The residue is chromatographed over silica gel using 5% $\text{MeOH}:\text{CH}_2\text{Cl}_2$ containing 0.5% NH_4OH to yield 0.086 g (94.5%) of titled product. The structure is supported by high resolution FAB mass spec.

35 Found: $[\text{m}^\cdot + \text{H}]^+$ at m/z 679; theory for $\text{C}_{33}\text{H}_{55}\text{N}_6\text{O}_7\text{S}$, 679.3861; Measured, 679.3861.

Preparation 2 N-tert-Butyloxyphenylalanine-p-nitro-phenyl ester (Formula B-2). Refer to Chart B.

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A cold solution (0°C) of Boc-Phenylalanine (17.5 g.), p-nitrophenol (10 g.) and dicyclohexylcarbodiimide (20.7 g.) in 100 ml of ethyl acetate is stirred for one hour. The mixture is filtered and filtrate is washed with water, 10% sodium bicarbonate solution, 5 saturated sodium chloride solution, dried (sodium sulfate) and concentrated in vacuo. The residue is triturated with ether and filtered to afford the title product.

Physical characteristics are as follows:

Anal. found: C, 62.37; H, 5.73; N, 7.21.

10 • FAB mass spec.: [m + H] at m/z 367.

Preparation 3 N-tert-Butyloxypheylalanine-histidine methyl ester (Formula B-3). Refer to Chart B.

A solution of Boc-Phe-p-nitrophenyl ester (2.5 g.) of Preparation 2, His-methyl ester hydrochloride (1.45 g.) and triethylamine (2 15 ml) in 10 ml of dimethylformamide is stirred at room temperature for 18 hours. The mixture is filtered and filtrate is diluted with ethyl acetate, washed with water, 10% sodium bicarbonate, saturated sodium chloride, dried (sodium sulfate) and concentrated in vacuo to afford the title product.

20 Physical characteristics are as follows:

Anal. found: C, 60.04; H, 7.04; N, 13.10.

FAB mass spec.: [m + H] at m/z 416.

Preparation 4 N-tert-Butyloxycarbonylphenylalanine-histidine(tosyl)-methyl ester (Formula B-4). Refer to Chart B.

25 A solution of Boc-Phe-His- OCH_3 (500 mg) of Preparation 3, tosyl chloride (230 mg) and triethylamine (120 mg) in 10 ml of methylene chloride is stirred at room temperature for one hour. The mixture is diluted with methylene chloride (30 ml) and washed with 10% sodium bicarbonate, water, saturated sodium chloride solution, dried (sodium 30 sulfate) and concentrated in vacuo to afford a white oil. The oil on trituration with hexane gives the white crystalline title product.

Physical characteristics are as follows:

Anal. found: C, 58.94; H, 6.24; N, 9.74; S, 5.62.

FAB mass spec.: [m + H] at m/z 571.

35 Preparation 5 N-tert-Butyloxycarbonylphenylalanine-histidine(tosyl) (Formula B-5). Refer to Chart B.

A solution of Boc-Phe-His(Tos)- OCH_3 (1 g.) of Preparation 4, lithium hydroxide (210 mg) in 10 ml of tetrahydrofuran:water (9:1) is

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stirred at room temperature for 30 min. The mixture is concentrated in vacuo, residual aqueous solution is poured onto ice, acidified with 3 N hydrochloric acid and extracted three times with 50 ml of ether. The ether solution is dried (sodium sulfate) and concentrated in vacuo to afford the title product as an amorphous solid.

Physical characteristics are as follows:

Anal. found: C, 57.63; H, 5.83; N, 9.87.

FAB mass spec.: [m + H] at m/z 557.

Example 15 Boc-Phe-His-Sta-Ile-NHOCH₃ (Formula C-5: R is methyl).

Refer to Chart C.

A. Boc-Ile-methylhydroxamate (Formula C-2: R is methyl).

To a solution of Boc Isoleucine (2.66 g.) and methylhydroxylamine hydrochloride (1.16 g.) in 50 ml of methylene chloride is added diethylcyanophosphonate (2.25 g.) and triethylamine (3.6 ml). The resulting solution is stirred at room temperature for 18 hours. The mixture is diluted with 50 ml of methylene chloride, washed two times with 100 ml of brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure to give a white solid. Recrystallization from diethyl ether gives the title product.

Physical characteristics are as follows:

M.p.: 119-121°C.

B. Boc-Sta-Ile-NHOCH₃ (Formula C-3: R is methyl).

A solution of Boc-Ile-NHOCH₃ (260 mg) of Part A in 5 ml of trifluoroacetic acid/methylene chloride (50%) is stirred at room temperature for 30 min. The solution is then concentrated in vacuo and residue is dissolved in methylene chloride (20 ml). To this solution is added Boc-Sta (275 mg), 1-hydroxybenzotriazole (135 mg), dicyclohexylcarbodiimide (415 mg) and triethylamine (200 mg) and the resulting solution is stirred for 18 hours. The above solution is filtered and washed with methylene chloride. The organic filtrates are combined and washed with 10% sodium bicarbonate, water, saturated sodium chloride solution, dried (sodium sulfate) and concentrated in vacuo to give an oil. The oil is purified by column chromatography on silica using ethyl acetate as eluent. This affords the title product as a white solid.

Physical characteristics are as follows:

FAB mas spec.: [m + H] at m/z 418.

C. Boc-Phe-His(Tos)-Sta-Ile-NHOCH₃ (Formula C-4: R is methyl).

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A solution of Boc-Sta-Ile-NHOCH₃ (100 mg) of Part B in 50% trifluoroacetic acid/methylene chloride is stirred for 30 min. The solution is then concentrated in vacuo and residue is dissolved in 5 ml of methylene chloride. To this solution is then added Boc-Phe-5 His(Tos)-COOH (130 mg), diethylcyanophosphonate (40 μ l) and triethylamine (50 μ l). The resulting solution is stirred at room temperature for 18 hours. The mixture is then diluted with 20 ml of methylene chloride and washed with 10% sodium bicarbonate, water, saturated sodium chloride solution, dried (sodium sulfate) and concentrated in vacuo giving 150 mg of crude solid. The solid is purified by column chromatography on silica gel using 4% methanol/chloroform as eluent and affords white crystalline title product.

Physical characteristics are as follows:

FAB mass spec.: $[m + H]$ at m/z 856.

15 D. Boc-Phe-His-Sta-Ile-NHOCH₃ (Formula C-5: R is methyl).

A solution of Boc-Phe-His(Tos)-Sta-Ile-NHOCH₃ (85 mg) of Part C and 1-hydroxybenzotriazole (40 mg) in 2 ml of methanol is stirred at room temperature for 72 hours. The mixture is diluted with 20 ml of methylene chloride, washed with 10% sodium bicarbonate, water, saturated sodium chloride solution, dried (sodium sulfate) and concentrated in vacuo to give 130 mg of crude oil. The oil on trituration with anhydrous ether gives the title product.

Physical characteristics are as follows:

FAB mass spec.: [m + H] at m/z 702.

25 Example 16 Boc-Phe-His-Sta-Ile-NHOCH₂-phenyl (Formula C-5: R is benzyl). Refer to Chart C.

A. Boc-Ile-Benzylhydroxamate (Formula C-2: R is benzyl).

To a solution of Boc-Ile (2.26 g.) and benzylhydroxylamine hydrochloride (2 g.) in 50 ml of methylene chloride is added diethyl-
 30 cyanophosphonate (2 g.) and triethylamine (3.5 ml). The resulting solution is stirred at room temperature for 18 hours. The mixture is diluted with 50 ml of methylene chloride, washed two times with 100 ml of brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure to give a crude oil. The oil is purified by column chromatography using 35% ethyl acetate/hexane as an eluent.
 35 This affords white crystalline title product.

Physical characteristics are as follows:

FAB mass spec.: [m + H] at m/z 337.

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B. Boc-Sta-Ile-NHOCH₂-phenyl (Formula C-3: R is benzyl).

A solution of Boc-Ile-NHOCH₂-phenyl (200 mg) of Part A in 5 ml of 50% trifluoroacetic acid/methylene chloride is stirred at room temperature for 30 min. The solution is then concentrated in vacuo and residue is dissolved in 5 ml of methylene chloride. To this solution is then added diethylcyanophosphonate (100 μ l), Boc-Sta (165 mg), triethylamine (200 μ l) and the resulting solution is stirred at room temperature for 18 hours. The mixture is diluted with 15 ml of methylene chloride and washed with water, saturated sodium chloride solution, dried (sodium sulfate) and concentrated in vacuo to give a crude yellow amorphous solid. This solid is purified by column chromatography on silica gel using 50% ethyl acetate/hexane as eluent. This affords a yellow solid title product.

Physical characteristics are as follows:

15 FAB mass spec.: [m + H] at m/z 494.

C. Boc-Phe-His(Tos)-Sta-Ile-NHOCH₂-phenyl (Formula C-4: R is benzyl).

A solution of Boc-Sta-Ile-NHOCH₂-phenyl (100 mg) of Part B in 50% trifluoroacetic acid/methylene chloride is stirred for 30 min. The solution is then concentrated in vacuo and the residue is dissolved in 5 ml of methylene chloride. To this solution is then added Boc-Phe-His(Tos)-COOH (110 mg), diethylcyanophosphonate (40 μ l) and triethylamine (50 μ l). The resulting solution is stirred at room temperature for 18 hours. The mixture is then diluted with 20 ml of methylene chloride and washed with 10% sodium bicarbonate, water, saturated sodium chloride solution, dried (sodium sulfate) and concentrated in vacuo giving a crude yellow oil. The oil is purified by column chromatography on silica gel using 4% methanol/chloroform as eluent and affords white crystalline title product.

30 Physical characteristics are as follows:

FAB mass spec.: [m + H] at m/z 932.

D. Boc-Phe-His-Sta-Ile-NHOCH₂-phenyl (Formula C-5: R is benzyl).

A solution of Boc-Phe-His(Tos)-Sta-Ile-NHOCH₂-phenyl (80 mg) of Part C and 1-hydroxybenzotriazole (40 mg) in 2 ml of methanol is stirred at room temperature for 72 hours. The mixture is diluted with 20 ml of methylene chloride, washed with 10% sodium bicarbonate, water, saturated sodium chloride solution, dried (sodium sulfate) and

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concentrated in vacuo to give a crude oil. The oil on trituration with anhydrous ether gives the title product.

Physical characteristics are as follows:

FAB mass spec.: $[m + H]$ at m/z 778.

5 Example 17 Boc-Phe-His-Sta-Ile-NHO-phenyl (Formula C-5: R is phenyl). Refer to Chart C.

A. Boc-Ile-phenylhydroxamate (Formula C-2: R is phenyl).

To a solution of Boc-Ile (2 g.) and phenylhydroxylamine hydrochloride (1.88 g.) in 50 ml of methylene chloride is added diethylcyanophosphonate (2 g.) and triethylamine (3.4 ml). The resulting solution is stirred at room temperature for 18 hours. The mixture is diluted with 50 ml of methylene chloride, washed two times with 100 ml of brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure to give an oil. The oil is purified by column chromatography on silica gel using 35% ethyl acetate/hexane as an eluent to afford white crystalline title product.

Physical characteristics are as follows:

FAB mass spec.: $[m + H]$ at m/z 323.

B. Boc-Sta-Ile-NHO-phenyl (Formula C-3: R is phenyl).

20 A solution of Boc-Ile-NHO-phenyl (322 mg) of Part A in 5 ml of trifluoroacetic acid/methylene chloride (50%) is stirred at room temperature for 30 min. The solution is then concentrated in vacuo and residue is dissolved in methylene chloride (20 ml). To this solution is added Boc-Sta (275 mg), 1-hydroxybenzotriazole (135 mg), 25 dicyclohexylcarbodiimide (415 mg) and triethylamine (200 mg) and the resulting solution is stirred for 18 hours. The solution is filtered and washed with methylene chloride. The organic filtrates are combined and washed with 10% sodium bicarbonate, water, saturated sodium chloride solution, dried (sodium sulfate) and concentrated in vacuo 30 to give an oil. The oil is purified by column chromatography on silica gel using 50% ethyl acetate/hexane as eluent. This affords the title product as a white solid.

Physical characteristics are as follows:

FAB mass spec.: $[m + H]$ at m/z 418.

35 C. Boc-Phe-His(Tos)-Sta-Ile-NHO-phenyl (Formula C-4: R is phenyl).

A solution of Boc-Sta-Ile-NHO-phenyl (125 mg) of Part B in 50% trifluoroacetic acid/methylene chloride is stirred for 30 min. The

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solution is then concentrated in vacuo and residue is dissolved in ml of methylene chloride. To this solution is then added Boc-Phe-His(Tos)-COOH (140 mg), diethylcyanophosphonate (40 μ l) and triethylamine (50 μ l). The resulting solution is stirred at room temperature 5 for 18 hours. The mixture is then diluted with 20 ml of methylene chloride and washed with 10% sodium bicarbonate, water, saturated sodium chloride solution, dried (sodium sulfate) and concentrated in vacuo giving a crude oil. The oil is purified by column chromatography on silica gel using 4% methanol/chloroform as eluent and 10 affords white crystalline title product.

Physical characteristics are as follows:

FAB mass spec.: [m + H] at m/z 918.

D. Boc-Phe-His-Sta-Ile-NHO-phenyl (Formula C-5: R is phenyl).

A solution of Boc-Phe-His(Tos)-Sta-Ile-NHO-phenyl (75 mg) of 15 Part C and 1-hydroxybenzotriazole (75 mg) in 2 ml of methanol is stirred at room temperature for 72 hours. The mixture is diluted with 20 ml of methylene chloride, washed with 10% sodium bicarbonate, water, saturated sodium chloride, dried (sodium sulfate) and concentrated in vacuo to give a crude oil. The oil on trituration with. 20 anhydrous ether gives the title product.

Physical characteristics are as follows:

FAB mass spec.: [m + H] at m/z 764.

Example 18 Boc-Phe-His-Sta-Ile-NHOEt (Formula C-5: R is ethyl).

Refer to Chart C.

A. Boc-Ile-ethylhydroxamate (Formula C-2: R is ethyl).

To a solution of Boc-Ile (2 g.) and ethylhydroxylamine hydrochloride (1.35 g.) in 50 ml of methylene chloride is added diethylcyanophosphonate (2 g.) and triethylamine (3.4 ml). The resulting solution is stirred at room temperature for 18 hours. The mixture is 30 diluted with methylene chloride (50 ml), washed two times with 100 ml of brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure to give an oil. The oil on trituration with ether/-hexane gives white crystalline title product.

Physical characteristics are as follows:

FAB mass spec.: [m + H] at m/z 278.

B. Boc-Sta-Ile-NHOC₂H₅ (Formula C-3: R is ethyl).

A solution of Boc-Ile-NHOC₂H₅ (275 mg) of Part A in 5 ml of trifluoroacetic acid/methylene chloride (50%) is stirred at room

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temperature for 30 min. The solution is then concentrated in vacuo and the residue is dissolved in methylene chloride (20 ml). To this solution is added Boc-Sta (275 mg), 1-hydroxybenzotriazole (135 mg), diecylohexylcarbodiimide (415 mg) and triethylamine (200 mg) and the 5 resulting solution is stirred for 18 hours. The solution is filtered and washed with methylene chloride. The organic filtrates are combined and washed with 10% sodium bicarbonate, water, saturated sodium chloride solution, dried (sodium sulfate) and concentrated in vacuo to give an oil. The oil is purified by column chromatography on 10 silica gel using 50% ethyl acetate/hexane as eluent. This affords the title product as a white solid.

Physical characteristics are as follows:

FAB mass spec.: [m + H] at m/z 432.

C. Boc-Phe-His(Tos)-Sta-Ile-NHOC₂H₅ (Formula C-4: R is ethyl).

15 A solution of Boc-Sta-Ile-NHOC₂H₅ (215 mg) of Part B in 50% trifluoroacetic acid/methylene chloride is stirred for 30 min. The solution is then concentrated in vacuo and residue is dissolved in 5 ml of methylene chloride. To this solution is then added Boc-Phe-His(Tos)-COOH (278 mg), diethylcyarophosphonate (80 μ l) and triethyl-20 amine (100 μ l). The resulting solution is stirred at room temperature for 18 hours. The mixture is then diluted with 20 ml of methylene chloride and washed with 10% sodium bicarbonate, water, saturated sodium chloride solution, dried (sodium sulfate) and concentrated in vacuo giving an oil. The oil is purified by column 25 chromatography on silica gel using 4% methanol/chloroform as eluent and affords white crystalline title product.

Physical characteristics are as follows:

FAB mass spec.: [m + H] at m/z 870.

D. Boc-Phe-His-Sta-Ile-NHOC₂H₅ (Formula C-5: R is ethyl).

30 A solution of Boc-Phe-His(Tos)-Sta-Ile-NHOC₂H₅ (100 mg) of Part C and 1-hydroxybenzotriazole (100 mg) in 5 ml of methanol is stirred at room temperature for 72 hours. The mixture is diluted with 20 ml of methylene chloride, washed with 10% sodium bicarbonate, water, saturated sodium chloride solution, dried (sodium sulfate) and concentrated in vacuo to give a crude oil. The oil on trituration with 35 anhydrous ether gives the title product.

Physical characteristics are as follows:

FAB mass spec.: [m + H] at m/z 716.

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FORMULAE

X-A₆-B₇-C₈-D₉-E₁₀-F₁₁-V

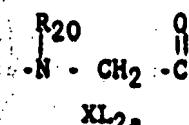
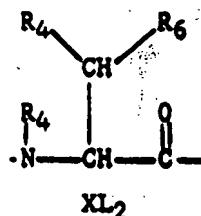
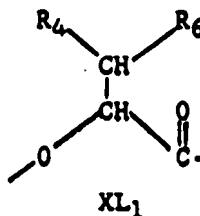
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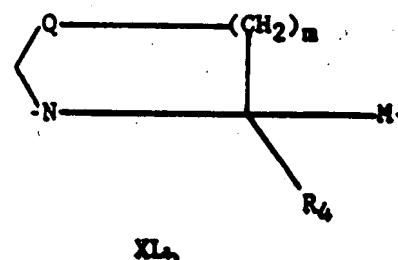
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II

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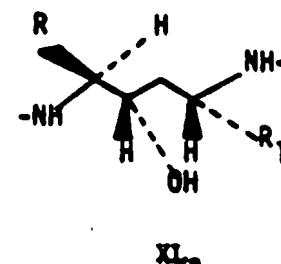
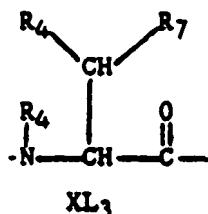


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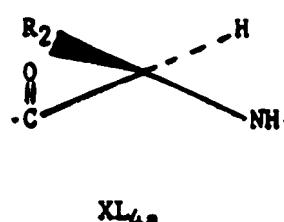
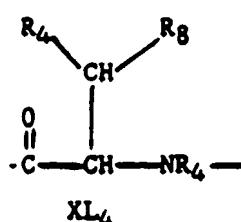


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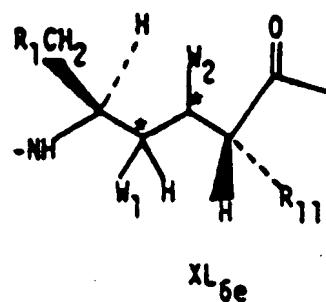
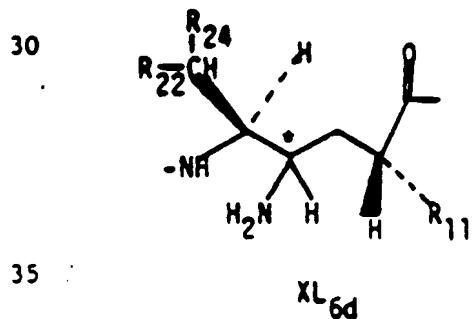
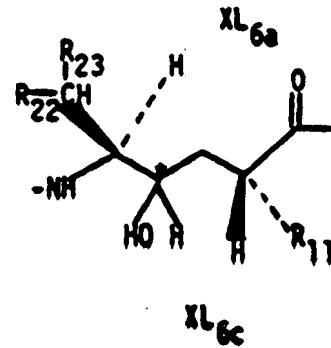
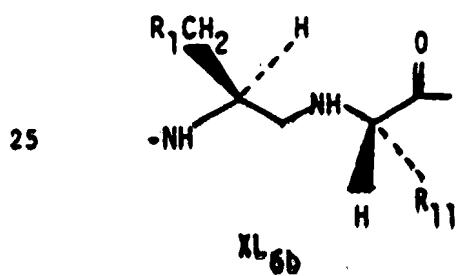
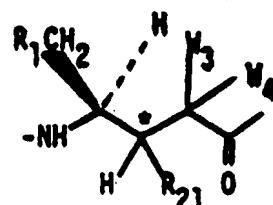
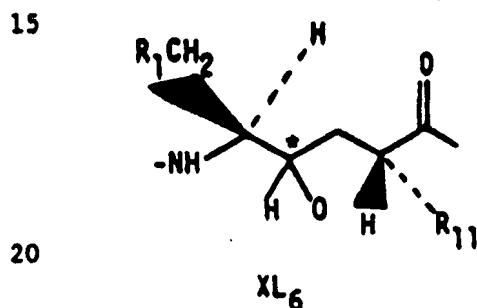
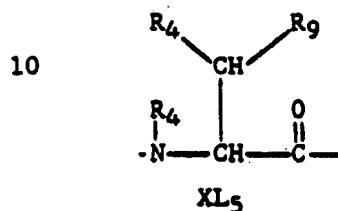
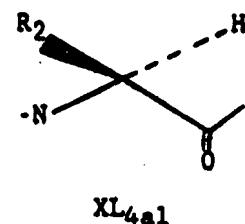
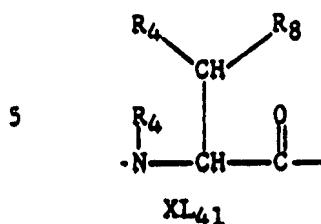
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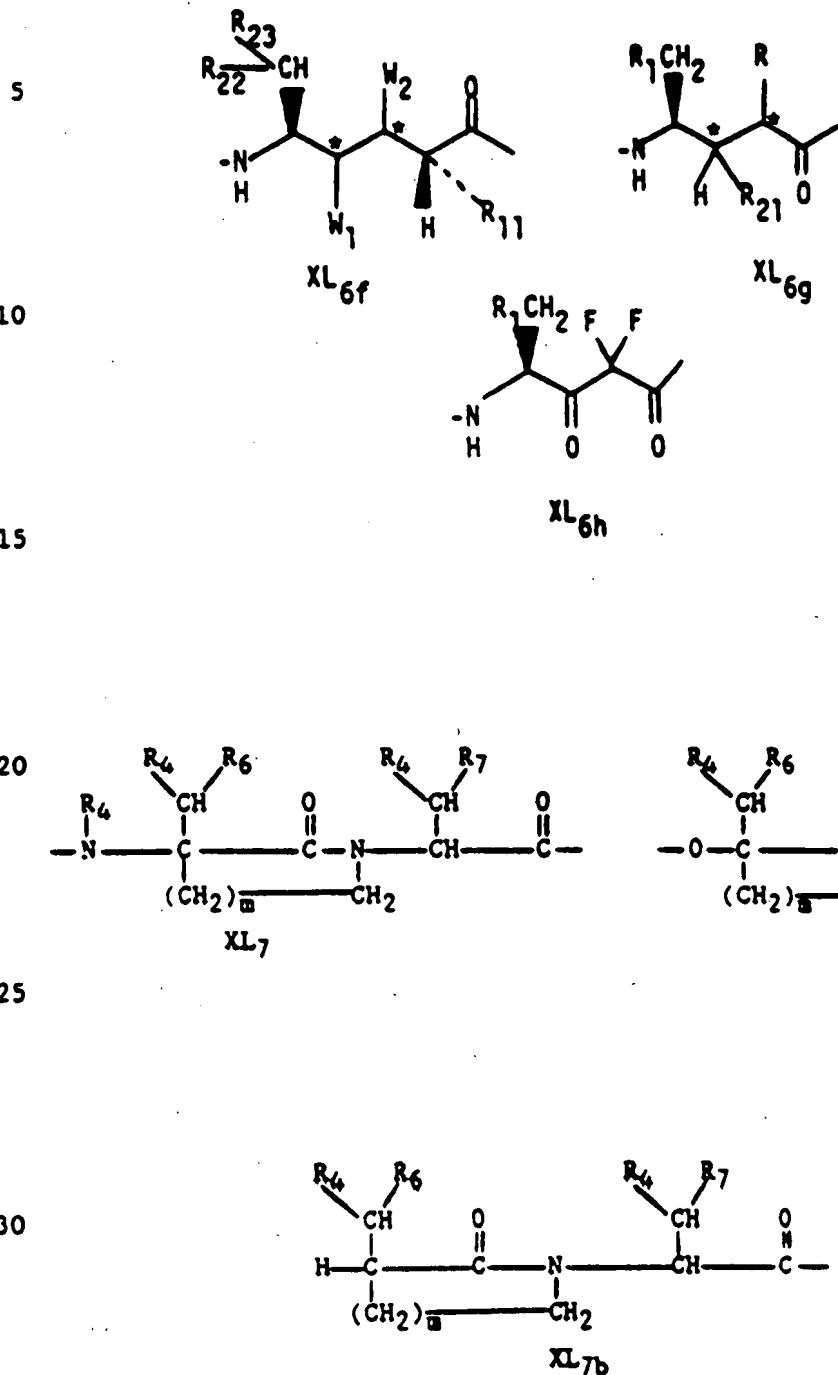
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FORMULAE (Continued)



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FORMULAE (Continued)

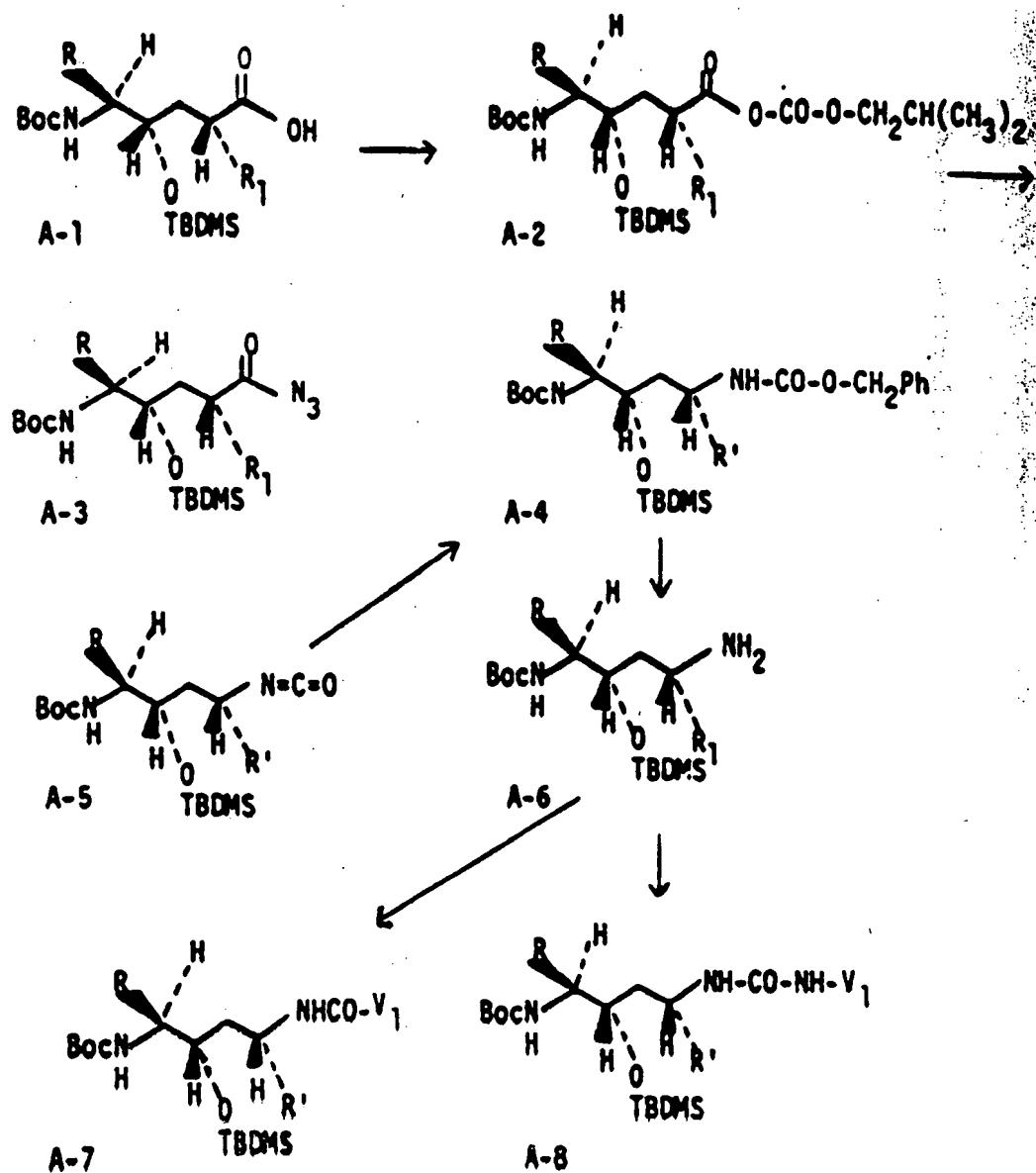


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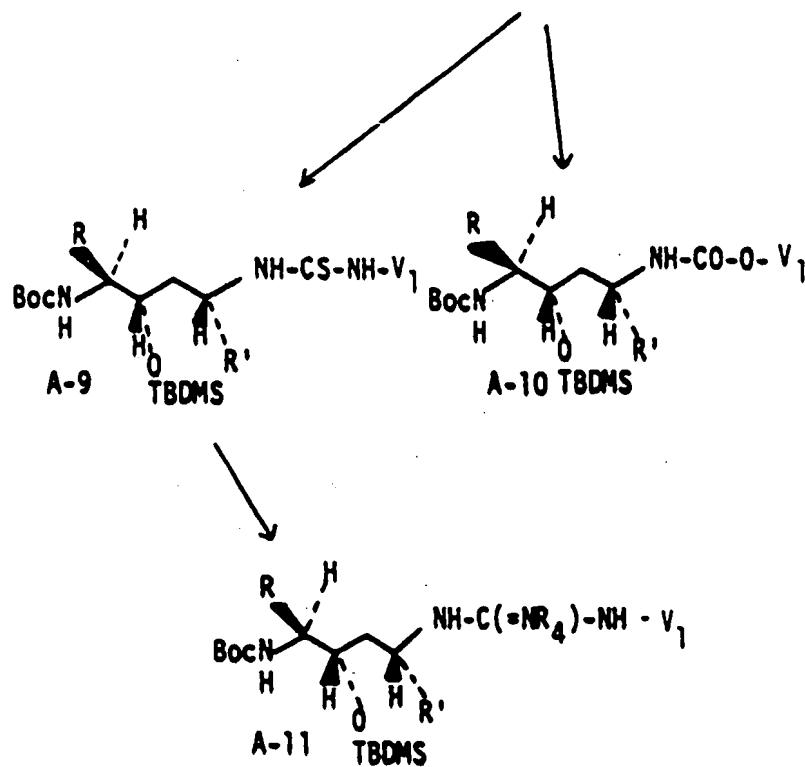
CHART A



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CHART A (continued)

From A-6

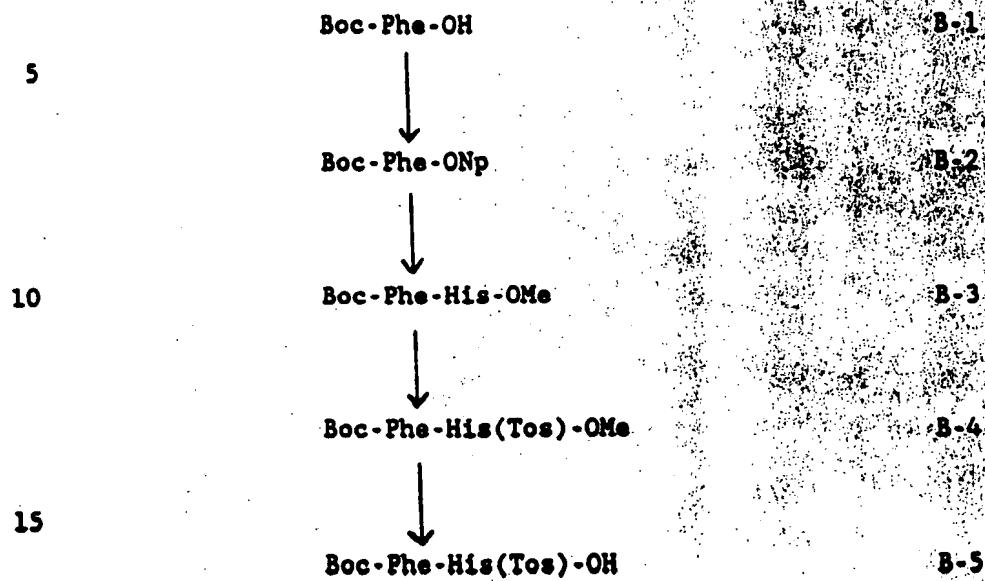


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CHART B



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CHART C

5

C-1

Boc - Ile - NHOR

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Boo-Sea-Il-NHOR

15

Boc-Phe-His(Tos)-Sta-Ile-NHOR

20

Boc-Phe-His-Sta-Ile-NHOBz

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30

35

C-2

C-3

C-4

C-5

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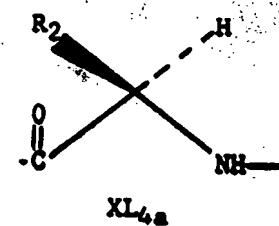
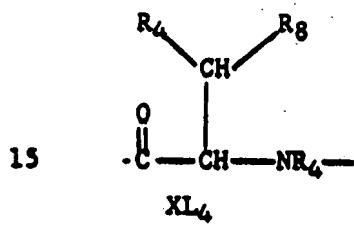
CLAIMS

1. A renin inhibitory peptide having a noncleavable transition state insert corresponding to the 10,11-position of the renin substrate (angiotensinogen) and having a moiety of the formula

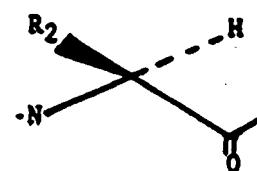
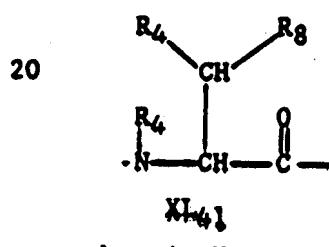
5 wherein V is

- C(-Y)-G₁₂-H₁₃-Z,
- W,
- G₁₂-H₁₃-W, or
- G₁₂₁-H₁₃₁-I₁₄-Z;

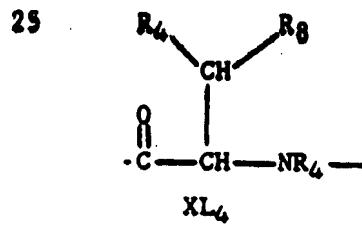
10 corresponding to positions 12 to 14 of the renin substrate, wherein G₁₂ is absent or a divalent moiety of the formula XL₄ or XL_{4a}



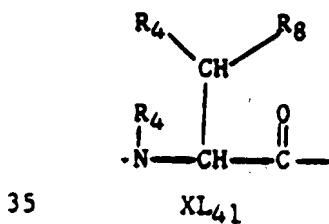
wherein G₁₂₁ is absent or a divalent moiety of the formula XL₄₁ or XL_{41a}



wherein H₁₃ is absent or a divalent moiety of the formula XL₄

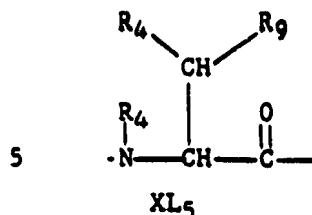


30 wherein H₁₃₁ is absent or a divalent moiety of the formula XL₄₁



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wherein I_{14} is absent or a divalent moiety of the formula XL_5



wherein W is

- (a) R_{14} ,
- (b) $-C(-Y)-CH_2-Y-R_5$,
- 10 (c) $-C(-Y)-YR_5$,
- (d) $-C(-Y)(CH_2)_n-R_5$,
- (e) $-C(-Y)-(CH_2)_nN-(R_4)_2$,
- (f) $-SO_2R_5$,
- (g) $-SO_2N(R_4)_2$,
- 15 (h) $-C(-Y)(CH_2)_2-SO_2R_5$,
- (i) $-C(-Y)-Y-(CH_2)_2-SO_2-R_5$,
- (j) $-C(-Y)-NR_4-O-R_5$,
- (k) $-C(-NCN)NHR_4$, or
- (l) $-C(-Y)(CH_2)_qC(-Y)YR_4$;

20 wherein each occurrence of Y may be the same or different and Y is

- (a) $-O-$,
- (b) $-S-$, or
- (c) $-NR_4-$;

wherein Z is

25

- (a) $-O-R_{10}$,
- (b) $-N(R_4)R_{14}$,
- (c) $-C_4-C_8$ cyclic amino, or
- (d) $-N(R_{10})(OR_{14})$;

wherein R_2 is

30

- (a) hydrogen, or
- (b) $-CH(R_3)R_4$;

wherein R_3 is

- (a) hydrogen,
- (b) hydroxy,
- 35 (c) C_1-C_5 alkyl,
- (d) C_3-C_7 cycloalkyl,
- (e) aryl,
- (f) $-Het$,

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- (g) C_1 - C_3 alkoxy, or
- (h) C_1 - C_3 alkylthio;

wherein R_4 at each occurrence is the same or different and is

- (a) hydrogen, or
- 5 (b) C_1 - C_5 alkyl;

wherein R_5 is

- (a) C_1 - C_6 alkyl,
- (b) C_3 - C_7 cycloalkyl,
- (c) aryl,
- 10 (d) -Het,
- (e) 5-oxo-2-pyrrolidinyl, or
- (f) - $C(CH_2OH)_3$;

wherein R_6 is

- (a) hydrogen,
- 15 (b) C_1 - C_5 alkyl,
- (c) hydroxy,
- (d) aryl,
- (e) -Het,
- (f) guanidinyl C_1 - C_3 alkyl.
- 20 (g) C_3 - C_7 cycloalkyl, or
- (h) -(CH_2)_p- C_3 - C_7 cycloalkyl;

wherein R_9 is

- (a) hydrogen,
- (b) hydroxy,
- 25 (c) amino C_1 - C_4 alkyl, or
- (d) guanidinyl- C_1 - C_3 alkyl;

wherein R_{10} is

- (a) hydrogen,
- (b) C_1 - C_5 alkyl,
- 30 (c) -(CH_2)_n R_{16} ,
- (d) -(CH_2)_n R_{17} ,
- (e) C_3 - C_7 cycloalkyl,
- (f) a pharmaceutically acceptable cation,
- (g) -(CHR_{25})- CH_2 - R_{15} , or
- 35 (h) - CH_2 -(CHR_{12})- R_{15} ;

wherein R_{12} is -(CH_2)_n- R_{13} ;

wherein R_{13} is

- (a) aryl,

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- (b) amino,
- (c) mono-, di- or tri- C_1 - C_3 alkylamino,
- (d) -Het,
- (e) C_1 - C_5 alkyl,
- 5 (f) C_3 - C_7 cycloalkyl,
- (g) C_2 - C_5 alkenyl,
- (h) C_3 - C_7 cycloalkenyl,
- (i) hydroxy,
- (j) C_1 - C_3 alkoxy,
- 10 (k) C_1 - C_3 alkanoyloxy,
- (l) mercapto,
- (m) C_1 - C_3 alkylthio,
- (n) -COOH,
- (o) -CO-O- C_1 - C_6 alkyl,
- 15 (p) -CO-O-CH₂-(C_1 - C_3 alkyl)-N(C_1 - C_3 alkyl)₂,
- (q) -CO-NR₂₂R₂₆,
- (r) C_4 - C_7 cyclic amino,
- (s) C_4 - C_7 cycloalkylamino,
- (t) guanidyl,
- 20 (u) cyano,
- (v) N-cyanoguanidyl,
- (w) cyanoamino,
- (x) (hydroxy C_2 - C_4 alkyl)amino,
- (y) di-(hydroxy C_2 - C_4 alkyl)amino, or
- 25 (z) -CO-NR₂₂R₂₅;

wherein R₁₄ is

- (a) hydrogen,
- (b) C_1 - C_{10} alkyl,
- (c) -(CH₂)_n-R₁₈,
- 30 (d) -(CH₂)_n-R₁₉,
- (e) -(CHR₂₅)-CH₂-R₁₅,
- (f) -CH₂-(CHR₁₂)-R₁₅,
- (g) (hydroxy C_1 - C_8 alkyl),
- (h) (C_1 - C_3 alkoxy) C_1 - C_8 alkyl,
- (i) -(CH₂)_n-aryl,
- (j) -(CH₂)_n-Het,
- (k) -(CH₂)_{n+2}-R₁₈, or
- (l) -(CH₂)_{n+2}-R₁₉;

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wherein R₁₅ is

- (a) hydroxy,
- (b) C₃-C₇cycloalkyl,
- (c) aryl,
- 5 (d) amino,
- (e) mono-, di-, or tri-C₁-C₃alkylamino,
- (f) mono- or di-(hydroxy C₂-C₄alkyl)amino,
- (g) -Het,
- (h) C₁-C₃alkoxy-,
- 10 (i) C₁-C₃alkanoyloxy-,
- (j) mercapto,
- (k) C₁-C₃alkylthio-,
- (l) C₁-C₅alkyl,
- (m) C₄-C₇cyclic amino,
- 15 (n) C₄-C₇cycloalkylamino,
- (o) C₂-C₅alkenyloxy, or
- (p) C₃-C₇cycloalkenyl;

wherein R₁₆ is

- (a) aryl,
- 20 (b) amino,
- (c) mono- or di-C₁-C₃alkylamino,
- (d) hydroxy,
- (e) C₃-C₇cycloalkyl,
- (f) C₄-C₇cyclic amino, or
- 25 (g) C₁-C₃alkanoyloxy;

wherein R₁₇ is

- (a) -Het,
- (b) C₂-C₅alkenyl,
- (c) C₃-C₇cycloalkenyl,
- 30 (d) C₁-C₃alkoxy,
- (e) mercapto,
- (f) C₁-C₃alkylthio,
- (g) -COOH,
- (h) -CO-O-C₁-C₆alkyl,
- (i) -CO-O-CH₂-(C₁-C₃alkyl)-N(C₁-C₃alkyl)₂,
- (j) -CO-NR₂₂R₂₆,
- (k) tri-C₁-C₃alkylamino,
- (l) guanidyl.

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- (m) cyano,
- (n) N-cyanoguanidyl,
- (o) (hydroxy C₂-C₄alkyl)amino, or
- (p) di-(hydroxy C₂-C₄alkyl)amino;

5 wherein R₁₈ is

- (a) amino,
- (b) mono-, or di-C₁-C₃alkylamino,
- (c) C₄-C₇cyclic amino, or
- (d) C₄-C₇cycloalkylamino;

10 wherein R₁₉ is

- (a) aryl,
- (b) -Het,
- (c) tri-C₁-C₃alkylamino,
- (d) C₃-C₇cycloalkyl,
- (e) C₂-C₅alkenyl,
- (f) C₃-C₇cycloalkenyl,
- (g) hydroxy,
- (h) C₁-C₃alkoxy,
- (i) C₁-C₃alkoxyloxy,

20 (j) mercapto,

- (k) C₁-C₃alkylthio,
- (l) -COOH,
- (m) -CO-O-C₁-C₆alkyl,
- (n) -CO-O-CH₂-(C₁-C₃alkyl)-N(C₁-C₃alkyl)₂.

25 (o) -CO-NR₂₂R₂₆,

- (p) C₄-C₇cycloalkylamino,

- (q) guanidyl,

- (r) cyano,

- (s) N-cyanoguanidyl,

30 (t) cyanoamino,

- (u) (hydroxy C₂-C₄alkyl)amino,

- (v) di-(hydroxy C₂-C₄alkyl)amino,

- (w) -SO₃H, or

- (x) -CO-NR₂₂R₂₅;

35 wherein R₂₂ is

- (a) hydrogen, or
- (b) C₁-C₃alkyl;

wherein R₂₅ is

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- (a) $-(\text{CH}_2)_n-\text{R}_{13}$,
- (b) hydrogen,
- (c) $\text{C}_1\text{-C}_3\text{alkyl}$, or
- (d) phenyl- $\text{C}_1\text{-C}_3\text{alkyl}$;

5 wherein R_{26} is

- (a) hydrogen,
- (b) $\text{C}_1\text{-C}_3\text{alkyl}$, or
- (c) phenyl- $\text{C}_1\text{-C}_3\text{alkyl}$;

wherein for each occurrence n is independently an integer of zero to
10 five inclusive;

wherein p is zero to 2, inclusive;

wherein q is 1 to 5, inclusive;

wherein aryl is phenyl or naphthyl substituted by zero to 3 of the
following:

- 15 (a) $\text{C}_1\text{-C}_3\text{alkyl}$,
- (b) hydroxy,
- (c) $\text{C}_1\text{-C}_3\text{alkoxy}$,
- (d) halo,
- (e) amino,
- 20 (f) mono- or di- $\text{C}_1\text{-C}_3\text{alkylamino}$,
- (g) $-\text{CHO}$,
- (h) $-\text{COOH}$,
- (i) COOR_{26} ,
- (j) CONHR_{26} ,
- 25 (k) nitro,
- (l) mercapto,
- (m) $\text{C}_1\text{-C}_3\text{alkylthio}$,
- (n) $\text{C}_1\text{-C}_3\text{alkylsulfinyl}$,
- (o) $\text{C}_1\text{-C}_3\text{alkylsulfonyl}$,
- 30 (p) $-\text{N}(\text{R}_4)\text{-C}_1\text{-C}_3\text{alkylsulfonyl}$,
- (q) SO_3H ,
- (r) SO_2NH_2 ,
- (s) $-\text{CN}$,
- (t) $-\text{CH}_2\text{NH}_2$,
- 35 (u) COOR_{25} , or
- (v) CONHR_{25} ;

wherein -Het is a 5- or 6-membered saturated or unsaturated ring
containing from one to three heteroatoms selected from the group

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consisting of nitrogen, oxygen, and sulfur; and including any bicyclic group in which any of the above heterocyclic rings is fused to a benzene ring, which heterocyclic moiety is substituted with zero to 3 of the following:

- 5 (i) $C_1\text{-}C_6$ alkyl,
- (ii) hydroxy,
- (iii) trifluoromethyl,
- (iv) $C_1\text{-}C_4$ alkoxy,
- (v) halo,
- 10 (vi) aryl,
- (vii) aryl $C_1\text{-}C_4$ alkyl-,
- (viii) amino, or
- (ix) mono- or di- $C_1\text{-}C_4$ alkylamino;
- 15 or a carboxy-, amino-, or other reactive group-protected form;
- 15 or a pharmaceutically acceptable acid addition salt thereof.

2. A renin inhibitory peptide of claim 1 of the formula I



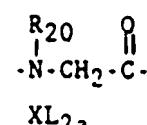
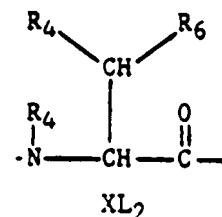
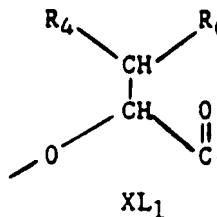
I

wherein X is

- 20 (a) hydrogen,
- (b) $C_1\text{-}C_5$ alkyl
- (c) $R_5\text{-}O\text{-}CH_2\text{-}C(O)\text{-}$,
- (d) $R_5\text{-}CH_2\text{-}O\text{-}C(O)\text{-}$,
- (e) $R_5\text{-}O\text{-}C(O)\text{-}$,
- 25 (f) $R_5\text{-}(CH_2)_n\text{-}C(O)\text{-}$,
- (g) $R_4N(R_4)\text{-}(CH_2)_n\text{-}C(O)$,
- (h) $R_5\text{-}SO_2\text{-}(CH_2)_q\text{-}C(O)\text{-}$, or
- (i) $R_5\text{-}SO_2\text{-}(CH_2)_q\text{-}O\text{-}C(O)\text{-}$;

wherein A_6 is absent or a divalent moiety of the formula XL_1 ,

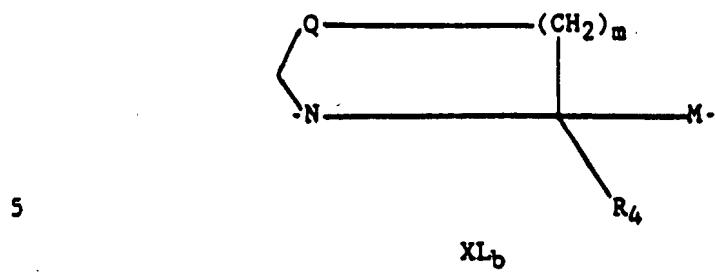
30 XL_2 , or XL_{2a}



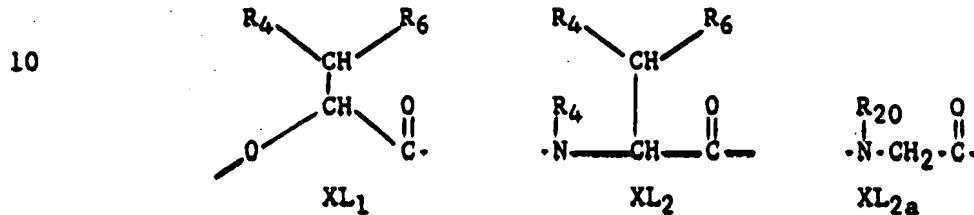
35 wherein B_7 is absent or a divalent moiety of the formula XL_b

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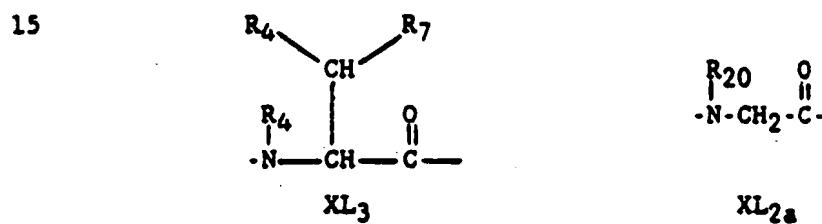
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wherein G_9 is absent or a divalent moiety of the formula XL_1 ,
 XL_2 , or XL_{2a} ;



wherein D_9 is a divalent moiety of the formula XL_3 or XL_{2a} ;



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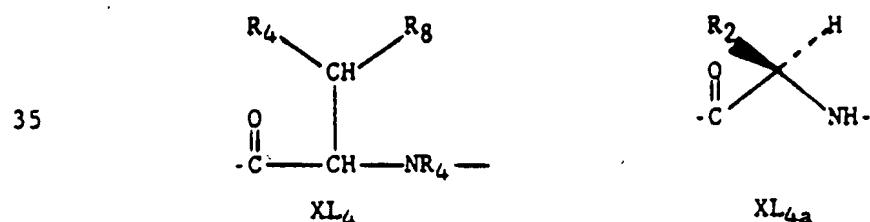
wherein $E_{10} \cdot F_{11}$ is a divalent moiety of the formula XL_a ,



wherein V is

- (a) $-C(-Y)-G_{12}-H_{13}-Z$,
- (b) $-W$, or
- 30 (c) $-G_{12}-H_{13}-W$;

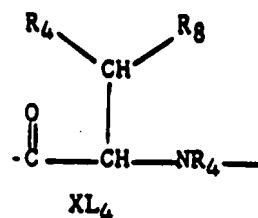
wherein G_{12} is absent or a divalent moiety of the formula XL_4 or
 XL_{4a}



wherein H_{13} is absent or a divalent moiety of the formula XL_4

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wherein W is

- (a) R_{14} ,
- (b) $-\text{C}(-\text{Y})-\text{CH}_2-\text{Y}-\text{R}_5$,
- (c) $-\text{C}(-\text{Y})-\text{YR}_5$,
- 10 (d) $-\text{C}(-\text{Y})(\text{CH}_2)_n-\text{R}_5$,
- (e) $-\text{C}(-\text{Y})-(\text{CH}_2)_n\text{N}-(\text{R}_4)_2$,
- (f) $-\text{SO}_2\text{R}_5$,
- (g) $-\text{SO}_2\text{N}(\text{R}_4)_2$,
- (h) $-\text{C}(-\text{Y})(\text{CH}_2)_2-\text{SO}_2\text{R}_5$,
- 15 (i) $-\text{C}(-\text{Y})-\text{Y}-(\text{CH}_2)_2-\text{SO}_2-\text{R}_5$,
- (j) $-\text{C}(-\text{Y})-\text{NR}_4-\text{O}-\text{R}_5$,
- (k) $-\text{C}(-\text{NCN})\text{NHR}_4$, or
- (l) $-\text{C}(-\text{Y})(\text{CH}_2)_q\text{C}(-\text{Y})\text{YR}_4$;

10

wherein each occurrence of Y may be the same or different and Y

20 is

- (a) $-\text{O}-$,
- (b) $-\text{S}-$, or
- (c) $-\text{NR}_4-$;

wherein Z is

- 25 (a) $-\text{O}-\text{R}_{10}$,
- (b) $-\text{N}(\text{R}_4)\text{R}_{14}$, or
- (c) $-\text{C}_4\text{-C}_8$ cyclic amino;

wherein R and R₁ are the same or different and are

- (a) $\text{C}_1\text{-C}_{10}$ alkyl,
- 30 (b) $\text{C}_3\text{-C}_{10}$ cycloalkyl,
- (c) aryl,
- (d) $\text{C}_1\text{-C}_{10}$ alkyl substituted by one or two
 - (1) hydroxy,
 - (2) $\text{C}_1\text{-C}_3$ alkoxy,
 - (3) $\text{C}_1\text{-C}_3$ alkylthio,
 - (4) aryl,
 - (5) $\text{C}_3\text{-C}_{10}$ cycloalkyl,
 - (6) Het.

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- (7) amino,
- (8) mono C₁-C₃ alkylamino,
- (9) di C₁-C₃ alkyl and amino.
- 5 (e) C₁-C₃alkoxy, or
- (f) C₁-C₃alkylthio;

wherein R₂ is

- (a) hydrogen, or
- (b) -CH(R₃)R₄;

wherein R₃ is

- 10 (a) hydrogen,
- (b) hydroxy,
- (c) C₁-C₅alkyl,
- (d) C₃-C₇cycloalkyl,
- (e) aryl,
- 15 (f) -Het,
- (g) C₁-C₃alkoxy, or
- (h) C₁-C₃alkylthio;

wherein R₄ at each occurrence is the same or different and is

- (a) hydrogen, or
- 20 (b) C₁-C₅alkyl;

wherein R₅ is

- (a) C₁-C₆alkyl,
- (b) C₃-C₇cycloalkyl,
- (c) aryl,
- 25 (d) -Het,
- (e) 5-oxo-2-pyrrolidinyl, or
- (f) -C(CH₂OH)₃;

wherein R₆ is

- (a) hydrogen,
- 30 (b) C₁-C₅alkyl,
- (c) -(CH₂)_p-aryl,
- (d) -(CH₂)_p-Het,
- (e) C₃-C₇cycloalkyl, or
- (f) 1- or 2-adamantyl;

35 wherein R₇ is

- (a) hydrogen,
- (b) C₁-C₅alkyl,
- (c) hydroxy,

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- (d) amino C_1 - C_4 alkyl-,
- (e) guanidinyl C_1 - C_3 alkyl-,
- (f) aryl,
- (g) -Het,
- 5 (h) methylthio,
- (i) C_3 - C_7 cycloalkyl, or
- (j) amino;

wherein R_8 is

- 10 (a) hydrogen,
- (b) C_1 - C_5 alkyl,
- (c) hydroxy,
- (d) aryl,
- (e) -Het,
- (f) guanidinyl C_1 - C_3 alkyl-, or
- 15 (g) C_3 - C_7 cycloalkyl;

wherein R_{10} is

- 20 (a) hydrogen,
- (b) C_1 - C_5 alkyl,
- (c) $-(CH_2)_nR_{16}$,
- (d) $-(CH_2)_nR_{17}$,
- (e) C_3 - C_7 cycloalkyl,
- (f) a pharmaceutically acceptable cation,
- (g) $-(CHR_{25})-CH_2-R_{15}$, or
- (h) $-CH_2-(CHR_{12})-R_{15}$;

25 wherein R_{12} is $-(CH_2)_n-R_{13}$;

wherein R_{13} is

- 30 (a) aryl,
- (b) amino,
- (c) mono-, di or tri- C_1 - C_3 alkylamino,
- (d) -Het,
- (e) C_1 - C_5 alkyl
- (f) C_3 - C_7 cycloalkyl,
- (g) C_2 - C_5 alkenyl,
- (h) C_3 - C_7 cycloalkenyl,
- (i) hydroxy,
- (j) C_1 - C_3 alkoxy,
- (k) C_1 - C_3 alkanoyloxy,
- (l) mercapto,

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- (m) C_1-C_3 alkylthio,
- (n) -COOH,
- (o) -CO-O- C_1-C_6 alkyl,
- (p) -CO-O-CH₂-(C_1-C_3 alkyl)-N(C_1-C_3 alkyl)₂,
- 5 (q) -CO-NR₂₂R₂₆;
- (r) C_4-C_7 cyclic amino,
- (s) C_4-C_7 cycloalkylamino,
- (t) guanidyl,
- (u) cyano,
- 10 (v) N-cyanoguanidyl,
- (w) cyanoamino,
- (x) (hydroxy C_2-C_4 alkyl)amino, or
- (y) di-(hydroxy C_2-C_4 alkyl)amino;

wherein R₁₄ is

- 15 (a) hydrogen,
- (b) C_1-C_{10} alkyl,
- (c) -(CH₂)_n-R₁₈,
- (d) -(CH₂)_n-R₁₉,
- (e) -(CHR₂₅)-CH₂-R₁₅,
- 20 (f) -CH₂-(CHR₁₂)-R₁₅,
- (g) (hydroxy C_1-C_8 alkyl), or
- (h) (C_1-C_3 alkoxy) C_1-C_8 alkyl;

wherein R₁₅ is

- 25 (a) hydroxy,
- (b) C_3-C_7 cycloalkyl,
- (c) aryl,
- (d) amino,
- (e) mono-, di-, or tri- C_1-C_3 alkylamino,
- (f) mono- or di-[hydroxy C_2-C_4 alkyl]amino,
- 30 (g) -Het,
- (h) C_1-C_3 alkoxy-,
- (i) C_1-C_3 alkanoyloxy-,
- (j) mercapto,
- (k) C_1-C_3 alkylthio-,
- 35 (l) C_1-C_5 alkyl,
- (m) C_4-C_7 cyclic amino,
- (n) C_4-C_7 cycloalkylamino,
- (o) C_2-C_5 alkenyloxy,

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(p) C_3 - C_7 cycloalkenyl;
wherein R_{16} is
(a) aryl,
(b) amino,
5 (c) mono- or di- C_1 - C_3 alkylamino,
(d) hydroxy,
(e) C_3 - C_7 cycloalkyl,
(f) C_4 - C_7 cyclic amino, or
(g) C_1 - C_3 alkanoyloxy;
10 wherein R_{17} is
(a) -Het,
(b) C_2 - C_5 alkenyl,
(c) C_3 - C_7 cycloalkenyl,
(d) C_1 - C_3 alkoxy,
15 (e) mercapto,
(f) C_1 - C_3 alkylthio,
(g) -COOH,
(h) -CO-O- C_1 - C_6 alkyl,
(i) -CO-O- CH_2 -(C_1 - C_3 alkyl)-N(C_1 - C_3 alkyl)₂,
20 (j) -CO-NR₂₂R₂₆,
(k) tri- C_1 - C_3 alkylamino,
(l) guanidyl,
(m) cyano,
(n) N-cyanoguanidyl,
25 (o) (hydroxy C_2 - C_4 alkyl)amino, or
(p) di-(hydroxy C_2 - C_4 alkyl)amino;
wherein R_{18} is
(a) amino,
(b) mono-, or di- C_1 - C_3 alkylamino, or
30 (c) C_4 - C_7 cyclic amino;
wherein R_{19} is
(a) aryl,
(b) -Het,
(c) tri- C_1 - C_3 alkylamino,
35 (d) C_3 - C_7 cycloalkyl,
(e) C_2 - C_5 alkenyl,
(f) C_3 - C_7 cycloalkenyl,
(g) hydroxy.

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- (h) $C_1\text{-}C_3\text{alkoxy}$,
- (i) $C_1\text{-}C_3\text{alkanoyloxy}$,
- (j) mercapto,
- (k) $C_1\text{-}C_3\text{alkylthio}$,
- (l) -COOH ,
- (m) $\text{-CO-O-C}_1\text{-C}_6\text{alkyl}$,
- (n) $\text{-CO-O-CH}_2\text{-(C}_1\text{-C}_3\text{alkyl)-N(C}_1\text{-C}_3\text{alkyl)}_2$,
- (o) $\text{-CO-NR}_{22}\text{R}_{26}$,
- (p) $C_4\text{-C}_7\text{cycloalkylamino}$,
- (q) guanidyl,
- (r) cyano,
- (s) $N\text{-cyanoguanidyl}$,
- (t) cyanoamino,
- (u) (hydroxy $C_2\text{-C}_4\text{alkyl}$)amino,
- 10 (v) di-(hydroxy $C_2\text{-C}_4\text{alkyl}$)amino; or
- (w) $\text{-SO}_3\text{H}$;

15 wherein R_{20} is

- (a) hydrogen,
- (b) $C_1\text{-C}_5\text{alkyl}$, or
- 20 (c) aryl- $C_1\text{-C}_5\text{alkyl}$;

wherein R_{22} is

- (a) hydrogen, or
- (b) $C_1\text{-C}_3\text{alkyl}$;

25 wherein R_{25} is $\text{-(CH}_2\text{)}_n\text{-R}_{13}$;

wherein R_{26} is

- (a) hydrogen,
- (b) $C_1\text{-C}_3\text{alkyl}$, or
- (c) phenyl- $C_1\text{-C}_3\text{alkyl}$;

30 wherein m is one or two;

wherein for each occurrence n is independently an integer of zero to five, inclusive;

35 wherein p is zero to 2 inclusive;

wherein q is 1 to 5, inclusive;

wherein Q is

- (a) $\text{-CH}_2\text{-}$,
- (b) -CH(OH)- ,
- (c) -O- , or
- (d) -S- ; and

wherein M is

- (a) -CO-, or
- (b) -CH₂-;

wherein aryl is phenyl or naphthyl substituted by zero to 3 to
5 the following:

- (a) C₁-C₃alkyl,
- (b) hydroxy,
- (c) C₁-C₃alkoxy,
- (d) halo,
- 10 (e) amino,
- (f) mono- or di-C₁-C₃alkylamino,
- (g) -CHO,
- (h) -COOH,
- (i) COOR₂₆,
- 15 (j) CONHR₂₆,
- (k) nitro,
- (l) mercapto,
- (m) C₁-C₃alkylthio,
- (n) C₁-C₃alkylsulfinyl,
- 20 (o) C₁-C₃alkylsulfonyl,
- (p) -N(R₄)-C₁-C₃alkylsulfonyl,
- (q) SO₃H,
- (r) SO₂NH₂,
- (s) -CN, or
- 25 (t) -CH₂NH₂;

wherein -Het is a 5- or 6-membered saturated or unsaturated ring containing from one to three heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur; and including any bicyclic group in which any of the above heterocyclic rings is fused
30 to a benzene ring, which heterocyclic moiety is substituted with zero to 3 of the following:

- (i) C₁-C₆alkyl,
- (ii) hydroxy,
- (iii) trifluoromethyl,
- 35 (iv) C₁-C₄alkoxy,
- (v) halo,
- (vi) aryl,
- (vii) aryl C₁-C₄alkyl.

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(viii) amino, and

(ix) mono- or di-C₁-C₄alkylamino;

with the overall provisos that

5 (1) R₁₆ or R₁₇ is an amino-containing substituent, hydroxy, mercapto, or -Het bonded through the hetero atom only when n for that substituent is an integer from two to five, inclusive;

10 (2) R₁₈ or R₁₉ is hydroxy, mercapto, or amino, or a mono-substituted nitrogen containing group bonded through the nitrogen only when n is not one;

15 (3) R₁₂ is -(CH₂)_n-R₁₃ and n is zero and both R₁₃ and R₁₅ are oxygen-, nitrogen-, or sulfur-containing substituents bonded through the hetero atom, only when the hetero atom is not also bonded to hydrogen;

20 (4) when R₁₂ is -(CH₂)_n-R₁₃ and n is zero, then R₁₃ and R₁₅ cannot both be -COOH;

(5) R₂₃ is -(CH₂)_n-R₁₃ and n is zero only when R₁₃ is other than a primary or secondary nitrogen-containing group hydroxy or mercapto group or when R₄ of -N(R₄)R₁₄ is other than hydrogen;

25 (6) R₁₇ or R₁₉ is -COOH only when n for that moiety is other than zero;

or a carboxy-, amino-, or other reactive group-protected form or a pharmaceutically acceptable acid addition salt thereof.

3. A compound of claim 2 selected from the group consisting of:

25 (3S,5S,6S)-3-(Benzylloxycarbonylamino)-6-[(N^a-(N^a-(t-butoxycarbonyl)-L-phenylalanyl)-L-histidyl)amino]-2,8-dimethyl-5-hydroxy-nonane;

(3S,5S,6S)-3-Amino-6-[(N^a-(N^a-(t-butoxycarbonyl)-L-phenylalanyl)-L-histidyl)amino]-2,8-dimethyl-5-hydroxynonane;

30 (3S,5S,6S)-6-[(N_a-(N^a-(t-Butoxycarbonyl)-L-phenylalanyl)-L-histidyl)amino]-2,8-dimethyl-5-hydroxy-3-[(isopropoxycarbonyl)amino]-nonane;

(3S,5S,6S)-6-[(N_a-(N^a-(t-Butoxycarbonyl)-L-phenylalanyl)-L-histidyl)amino]-2,8-dimethyl-5-hydroxy-3-[(3-methyl-1-oxybutyl)amino]-nonane;

(3S,5S,6S)-3-[(N_a-(Benzylloxycarbonyl)-D-valyl)amino]-6-[(N_a-(N^a-(t-butoxycarbonyl)-L-phenylalanyl)-L-histidyl)amino]-2,8-dimethyl-5-hydroxynonane;

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(3S,5S,6S)-6-[(N²-(t-Butoxycarbonyl)-L-phenylalanyl)-L-histidyl]amino]-2,8-dimethyl-5-hydroxy-3-[(D-valyl)amino]nonane;

(3S,5S,6S)-3-[(N²-(3-Aminomethyl)benzoyl)-D-valyl]amino]-6-[(N²-(t-Butoxycarbonyl)-L-phenylalanyl)-L-histidyl]amino]-2,8-dimethyl-5-hydroxynonane;

(3S,5S,6S)-6-[(N²-(t-Butoxycarbonyl)-L-phenylalanyl)-L-histidyl]amino]-2,8-dimethyl-5-hydroxy-3-[(N²-(2-pyridinyl)ethanoyl-D-valyl)amino]nonane;

(3S,5S,6S)-6-[(N²-(N²-(tert-Butoxycarbonyl)-L-phenylalanyl)-L-histidyl)amino]-2,8-dimethyl-5-hydroxy-3-[(isobutoxycarbonyl)amino]nonane;

(3S,5S,6S)-6-[(N²-(N²-(tert-Butoxycarbonyl)-L-phenylalanyl)-L-histidyl)amino]-2,8-dimethyl-5-hydroxy-3-[(isopropylamino)carbonyl]amino]nonane;

(3S,5S,6S)-6-[(N²-(N²-(tert-Butoxycarbonyl)-L-phenylalanyl)-L-histidyl)amino]-2,8-dimethyl-5-hydroxy-3-[(methoxyamino)carbonyl]amino]nonane;

(3S,5S,6S)-6-[(N²-(N²-(tert-Butoxycarbonyl)-L-phenylalanyl)-L-histidyl)amino]-2,8-dimethyl-5-hydroxy-3-[(propylamino)thiocarbonyl]amino]nonane;

(3S,5S,6S)-6-[(N²-(N²-(tert-Butoxycarbonyl)-L-phenylalanyl)-L-histidyl)amino]-2,8-dimethyl-3-[(N,N-dimethylsulfamoyl)amino]-5-hydroxynonane; and

(3S,5S,6S)-6-[(N²-(N²-(tert-Butoxycarbonyl)-L-phenylalanyl)-L-histidyl)amino]-3-[(ethanesulfonyl)amino]-2,8-dimethyl-5-hydroxy-nonane.

4. A compound of Claim 2, wherein V is W, W is -C(=Y)-YR₅ or -C(=Y)-NR₄-O-R₅, and Y is -O- or -S-.

30

5. A compound of Claim 4 selected from

(3S,5S,6S)-6-[(N²-(tert-Butoxycarbonyl)-L-phenylalanyl)-L-histidyl]amino]-2,8-dimethyl-5-hydroxy-3-[(isobutoxycarbonyl)amino]nonane;

35

(3S,5S,6S)-6-[(N²-(tert-Butoxycarbonyl)-L-phenylalanyl)-L-histidyl]amino]-2,8-dimethyl-5-hydroxy-3-[(isopropylamino)carbonyl]amino]nonane; and

(3S,5S,6S)-6-[(N²-(tert-Butoxycarbonyl)-L-phenylalanyl)-L-

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histidyl]amino]-2,8-dimethyl-5-hydroxy-3-[(methoxyamino)carbonyl]amino]nonane.

6. A renin inhibitory peptide of claim 1 of the formula II

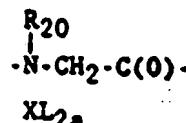
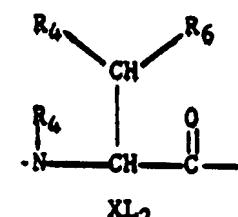
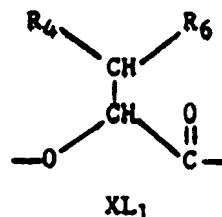
5 X-A₆-B₇-C₈-D₉-E₁₀-F₁₁-G₁₂-H₁₃-I₁₄-Z

wherein X is

- 10 (a) hydrogen,
- (b) C₁-C₅alkyl
- (c) R₅-O-CH₂-C(=O)-,
- (d) R₅-CH₂-O-C(=O)-,
- (e) R₅-O-C(=O)-,
- (f) R₅-(CH₂)_n-C(=O)-,
- (g) R₄N(R₄)-(CH₂)_n-C(=O)-,
- (h) R₅-SO₂-(CH₂)_q-C(=O)-,
- (i) R₅-SO₂-(CH₂)_q-O-C(=O)-,
- (j) R₆-(CH₂)₁-C(=O)-, or
- (k) [R₆-(CH₂)_n]₂CH-C(=O)-;

wherein A₆ is absent or a divalent moiety of the formula XL₁, XL₂, or XL_{2a}

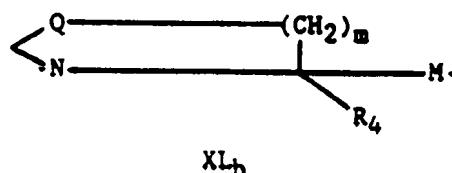
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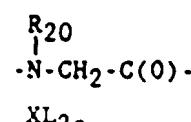
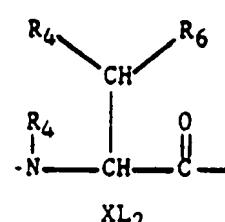
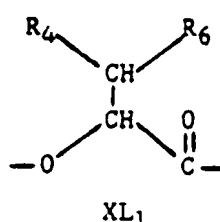
wherein B₇ is absent or a divalent moiety of the formula XL_b

30



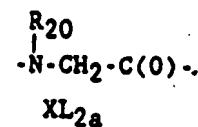
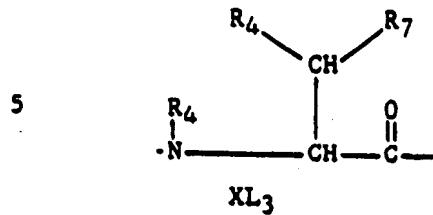
wherein C₈ is absent or a divalent moiety of the formula XL₁, XL₂ or XL_{2a}

35

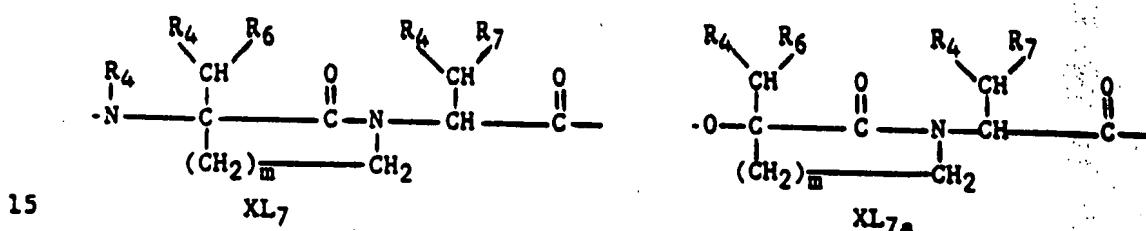


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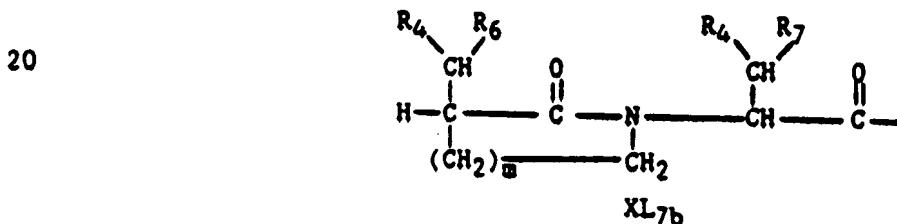
wherein D₉ is a divalent moiety of the formula XL₃ or XL_{2a}



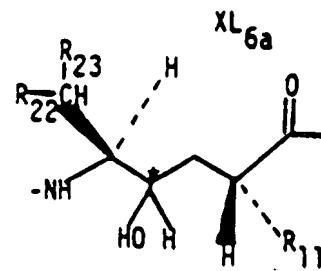
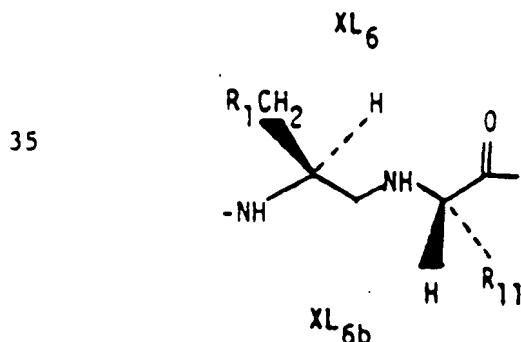
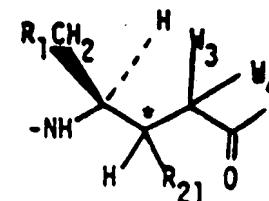
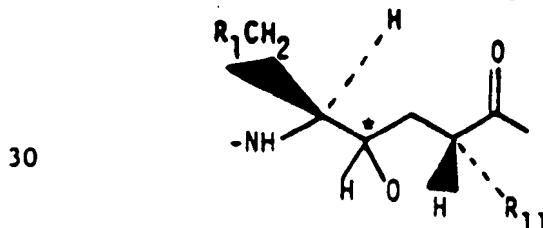
or wherein C₈-D₉ is a divalent moiety of the formula XL₇ or
10 XL_{7a},



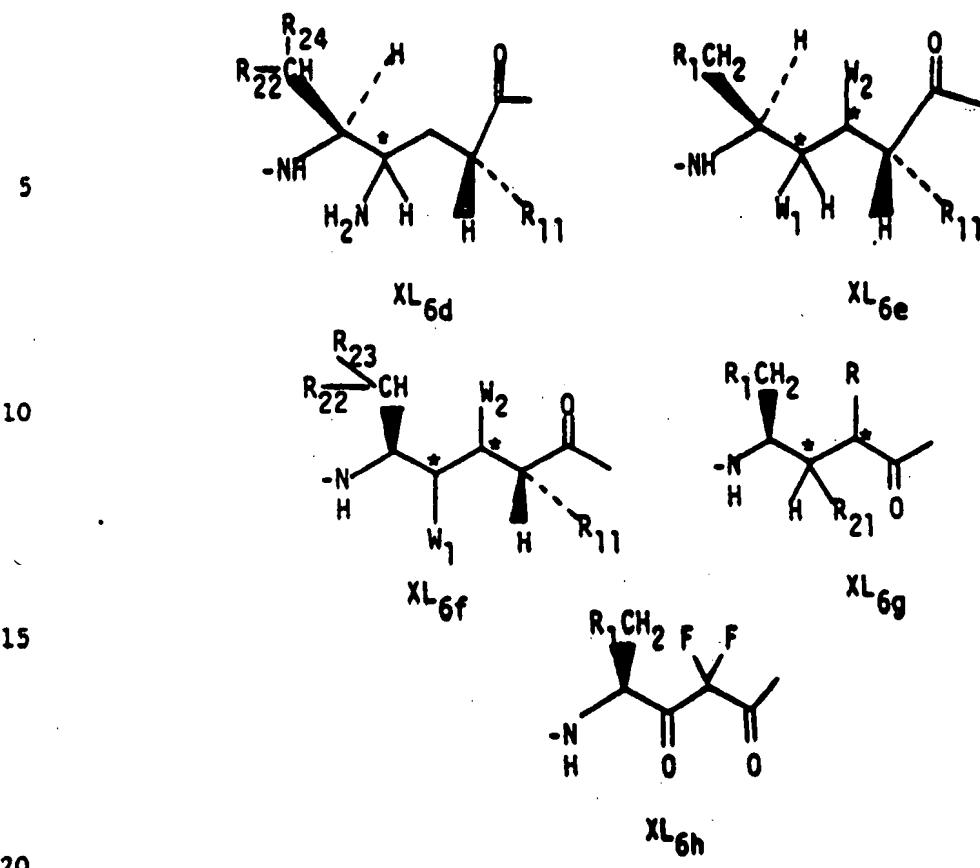
or wherein C₈-D₉ is a monovalent moiety of the formula XL_{7b} when
X, A₆, and B₇ are all absent;



25 wherein E₁₀-F₁₁ is a divalent moiety of the formula XL₆, XL_{6a},
XL_{6b}, XL_{6c}, XL_{6d}, XL_{6e}, XL_{6f}, XL_{6g} or XL_{6h}:



-78-

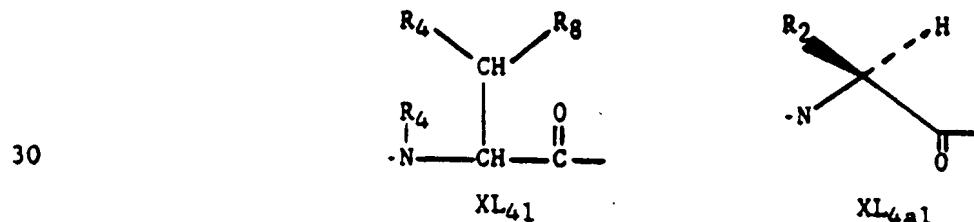


wherein * indicates an asymmetric center which is either in the R or S configuration;

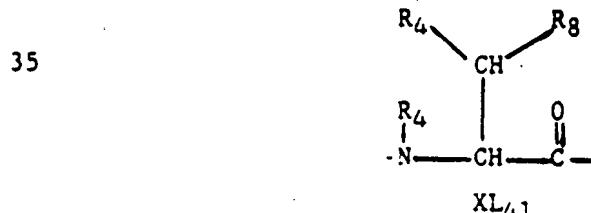
wherein W₁ and W₂ are -OH or -NH₂;

wherein W₃ and W₄ are -H or -F;

25 wherein G₁₂₁ is absent or a divalent moiety of the formula XL₄₁ or XL_{4a1}:



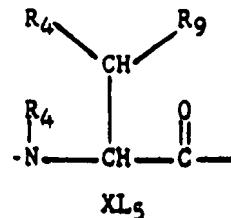
wherein H₁₃₁ is absent or a divalent moiety of the formula XL₄₁:



.7.)

wherein I₁₄ is absent or a divalent moiety of the formula XL₅;

5



wherein Z is -N(R₁₀)(OR₁₄);

10 wherein R is

- (a) isopropyl,
- (b) isobutyl,
- (c) phenylmethyl, or
- (d) -(CH₂)_p-C₃-C₇cycloalkyl;

15 wherein R₁ is

- (a) hydrogen,
- (b) C₁-C₅alkyl,
- (c) aryl,
- (d) C₃-C₇cycloalkyl,
- (e) -Het,
- (f) C₁-C₃alkoxy, or
- (g) C₁-C₃alkylthio;

wherein R₂ is

- (a) hydrogen, or
- (b) -CH(R₃)R₄;

25 wherein R₃ is

- (a) hydrogen,
- (b) hydroxy,
- (c) C₁-C₅alkyl,
- (d) C₃-C₇cycloalkyl,
- (e) aryl,
- (f) -Het,
- (g) C₁-C₃alkoxy, or
- (h) C₁-C₃alkylthio;

30 wherein R₄ at each occurrence is the same or different and is

- (a) hydrogen, or
- (b) C₁-C₅alkyl;

wherein R₅ is

-8-

- (a) C_1 - C_6 alkyl,
- (b) C_3 - C_7 cycloalkyl,
- (c) aryl,
- (d) -Het, or
- (e) 5-oxo-2-pyrrolidinyl;

5

wherein R_6 is

- (a) hydrogen,
- (b) C_1 - C_5 alkyl,
- (c) $-(CH_2)_p$ -aryl,
- (d) $-(CH_2)_p$ -Het,
- (e) $-(CH_2)_p$ - C_3 - C_7 cycloalkyl, or
- (f) 1- or 2-adamantyl;

10

wherein R_7 is

- (a) hydrogen,
- (b) C_1 - C_5 alkyl,
- (c) hydroxy,
- (d) amino C_1 - C_4 alkyl-,
- (e) guanidinyl C_1 - C_3 alkyl-,
- (f) aryl,
- (g) -Het,
- (h) methylthio,
- (i) $-(CH_2)_p$ - C_3 - C_7 cycloalkyl, or
- (j) amino;

20

wherein R_8 is

- (a) hydrogen,
- (b) C_1 - C_5 alkyl,
- (c) hydroxy,
- (d) aryl,
- (e) -Het,
- (f) guanidinyl- C_1 - C_3 alkyl-, or
- (g) $-(CH_2)_p$ - C_3 - C_7 cycloalkyl;

30

wherein R_9 is

35

- (a) hydrogen,
- (b) hydroxy,
- (c) amino C_1 - C_4 alkyl-, or
- (d) guanidinyl- C_1 - C_3 alkyl-;

wherein R_{10} is

- (a) hydrogen, or

.81.

(b) $C_1\text{-}C_5\text{alkyl}$;wherein R_{11} is -R or -R₂;wherein R_{13} is

(a) aryl,

5

(b) amino,

(c) mono-, di or tri- $C_1\text{-}C_3\text{alkylamino}$,

(d) -Het,

(e) $C_1\text{-}C_5\text{alkyl}$ (f) $C_3\text{-}C_7\text{cycloalkyl}$,

10

(g) $C_2\text{-}C_5\text{alkenyl}$,(h) $C_3\text{-}C_7\text{cycloalkenyl}$,

(i) hydroxy,

(j) $C_1\text{-}C_3\text{alkoxy}$,(k) $C_1\text{-}C_3\text{alkanoyloxy}$,

15

(l) mercapto,

(m) $C_1\text{-}C_3\text{alkylthio}$,

(n) -COOH,

(o) -CO-O-C₁-C₆alkyl,(p) -CO-O-CH₂-(C₁-C₃alkyl)-N(C₁-C₃alkyl)₂,

20

(q) -CO-NR₂₂R₂₅;(r) $C_4\text{-}C_7\text{cyclic amino}$,(s) $C_4\text{-}C_7\text{cycloalkylamino}$,

(t) guanidyl,

(u) cyano,

25

(v) N-cyanoguanidyl,

(w) cyanoamino,

(x) (hydroxy-C₂-C₄alkyl)amino, or(y) di-(hydroxy-C₂-C₄alkyl)amino;wherein R_{14} is

30

(a) $C_1\text{-}C_{10}\text{alkyl}$,(b) -(CH₂)_n-aryl,(c) -(CH₂)_n-Het,(d) -(CH₂)_{n+2}-R₁₈,(e) -(CH₂)_{n+2}-R₁₉,

35

(f) (hydroxy-C₁-C₈alkyl), or(g) (C₁-C₃alkoxy)C₁-C₈alkyl;wherein R_{18} is

(a) amino.

.87.

(b) mono-, or di- C_1 - C_3 alkylamino,(c) C_4 - C_7 cyclic amino; or(d) C_4 - C_7 cycloalkylamino;wherein R_{19} is

5

(a) aryl,

(b) -Het,

(c) tri- C_1 - C_3 alkylamino,(d) C_3 - C_7 cycloalkyl,(e) C_2 - C_5 alkenyl,

10

(f) C_3 - C_7 cycloalkenyl,

(g) hydroxy,

(h) C_1 - C_3 alkoxy,(i) C_1 - C_3 alkanoyloxy,

(j) mercapto,

15

(k) C_1 - C_3 alkylthio,

(l) -COOH,

(m) -CO-O- C_1 - C_6 alkyl,(n) -CO-O-CH₂-(C_1 - C_3 alkyl)-N(C_1 - C_3 alkyl)₂,(o) -CO-NR₂₂R₂₅,

20

(p) guanidyl,

(q) cyano,

(r) N-cyanoguanidyl,

(s) cyanoamino,

(t) (hydroxy- C_2 - C_4 alkyl)amino,

25

(u) di-(hydroxy- C_2 - C_4 alkyl)amino; or(v) -SO₃H;wherein R_{20} is

(a) hydrogen,

(b) C_1 - C_5 alkyl, or

30

(c) aryl- C_1 - C_5 alkyl;wherein R_{21} is(a) -NH₂, or

(b) -OH;

wherein R_{22} is

35

(a) hydrogen, or

(b) C_1 - C_3 alkyl;wherein R_{23} is(a) -(CH₂)_n-OH,

.83

(b) $-(\text{CH}_2)_n\text{NH}_2$,

(c) aryl, or

(d) $\text{C}_1\text{-C}_3\text{alkyl}$;wherein R_{24} is $-(\text{CH}_2)_n\text{R}_{13}$;5 wherein R_{25} is

(a) hydrogen,

(b) $\text{C}_1\text{-C}_3\text{alkyl}$, or(c) phenyl- $\text{C}_1\text{-C}_3\text{alkyl}$;wherein i is zero to two, inclusive;10 wherein m is one or two;wherein for each occurrence n is independently an integer of zero to five, inclusive;wherein p is zero to 2, inclusive;wherein q is 1 to 5, inclusive;15 wherein Q is(a) $-\text{CH}_2-$,(b) $-\text{CH}(\text{OH})-$,(c) $-\text{O}-$, or(d) $-\text{S}-$;20 wherein M is(a) $-\text{CO}-$, or(b) $-\text{CH}_2-$;

wherein aryl is phenyl or naphthyl substituted by zero to 3 of the following:

25 (a) $\text{C}_1\text{-C}_3\text{alkyl}$,

(b) hydroxy,

(c) $\text{C}_1\text{-C}_3\text{alkoxy}$,

(d) halo,

(e) amino,

30 (f) mono- or di- $\text{C}_1\text{-C}_3\text{alkylamino}$,(g) $-\text{CHO}$,(h) $-\text{COOH}$,(i) COOR_{25} ,(j) CONHR_{25} ,

35 (k) nitro,

(l) mercapto,

(m) $\text{C}_1\text{-C}_3\text{alkylthio}$,(n) $\text{C}_1\text{-C}_3\text{alkylsulfinyl}$.

.4.

- (o) $C_1\text{-}C_3\text{alkylsulfonyl}$,
- (p) $\text{-N}(R_4)\text{-}C_1\text{-}C_3\text{alkylsulfonyl}$,
- (q) SO_3H ,
- (r) SO_2NH_2 ,
- 5 (s) -CN , or
- (t) $\text{-CH}_2\text{NH}_2$;

wherein -Het is a 5- or 6-membered saturated or unsaturated ring containing from one to three heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur; and including any 10 bicyclic group in which any of the above heterocyclic rings is fused to a benzene ring, which heterocyclic moiety is substituted with zero to 3 of the following:

- 15 (i) $C_1\text{-}C_6\text{alkyl}$,
- (ii) hydroxy,
- (iii) trifluoromethyl,
- (iv) $C_1\text{-}C_4\text{alkoxy}$,
- (v) halo,
- (vi) aryl,
- (vii) aryl- $C_1\text{-}C_4\text{alkyl}$ -,
- 20 (viii) amino, or
- (ix) mono- or di- $C_1\text{-}C_4\text{alkylamino}$;

with the overall provisos that

- (1) when R_{14} is $C_1\text{-}C_3$ alkyl, $E_{10}\text{-}F_{11}$ does not include XL_6 , XL_{6a} , XL_{6b} , XL_{6c} , XL_{6d} , XL_{6e} or XL_{6f} ;
- 25 (2) when R_{14} is $C_1\text{-}C_3$ alkyl, $C_8\text{-}D_9$ does not include XL_7 , XL_{7a} or XL_{7b} ;
- (3) when R_{10} is $C_1\text{-}C_5$ alkyl, one of G_{121} , H_{131} or I_{14} must be present;
- (4) when X is $R_5\text{-CH}_2\text{-O-C(O)-}$ and only D_9 , E_{10} and F_{11} are 30 present, R_5 is other than phenyl;
or a carboxy-, amino-, or other reactive group-protected form thereof;
or a pharmaceutically acceptable acid addition salt thereof.

35 7. A renin inhibitory peptide of claim 6

wherein X is

- (a) $R_5\text{-O-CH}_2\text{-C(O)-}$,
- (b) $R_5\text{-CH}_2\text{-O-C(O)-}$.

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(c) $R_5 \cdot (CH_2)_n \cdot C(O) \cdot$,
 (d) $R_6 \cdot (CH_2)_i \cdot C(O) \cdot$, or
 (e) $[R_6 \cdot (CH_2)_n]_2 CH \cdot C(O) \cdot$;

wherein A_6 is absent or a divalent moiety of the formula XL_2

5

10

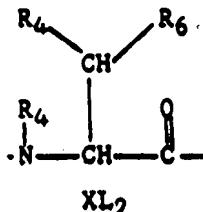
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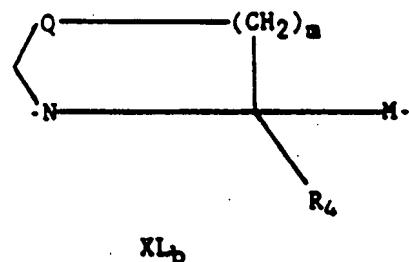
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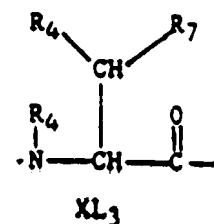
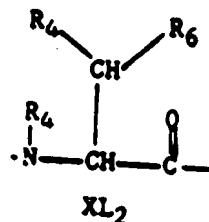
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wherein B_7 is absent or a divalent moiety of the formula XL_b



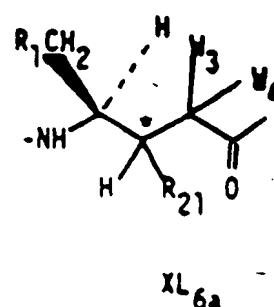
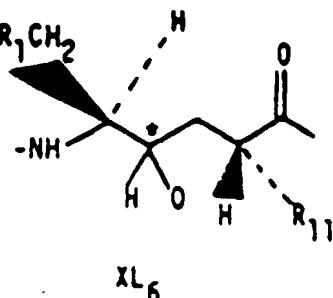
wherein C_8 is absent or a divalent moiety of the formula XL_2



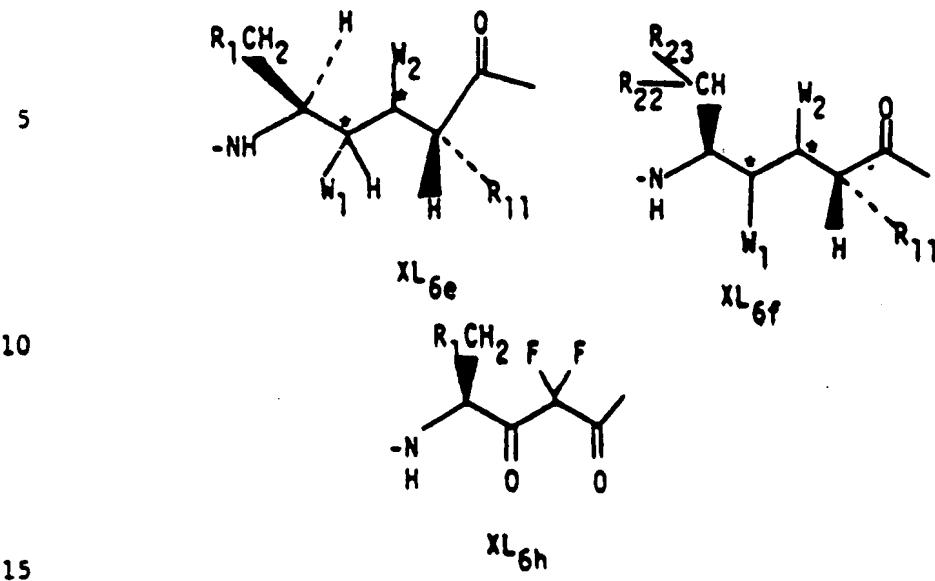
wherein $E_{10} \cdot F_{11}$ is a divalent moiety of the formula XL_6 , XL_{6a} , XL_{6e} , XL_{6f} or XL_{6h}

35

2311



-CS-



wherein * indicates an asymmetric center which is either in the
20 R or S configuration;

wherein W₁ and W₂ are -OH or -NH₂;

wherein W₃ and W₄ are -H or -F;

wherein G₁₂₁ is absent or a divalent moiety of the formula XL₄₁



30 wherein H₁₃₁ is absent or a divalent moiety of the formula XL₄₁



wherein I₁₄ is absent;

wherein Z is -N(R₁₀)(OR₁₄);

-87-

wherein R is

- (a) isopropyl,
- (b) isobutyl,
- (c) phenylmethyl, or
- 5 (d) -(CH₂)_p-C₃-C₇ cycloalkyl;

wherein R₁ is

- (a) C₁-C₅ alkyl,
- (b) aryl, or
- (c) C₃-C₇ cycloalkyl;

10 wherein R₄ at each occurrence is the same or different and is

- (a) hydrogen, or
- (b) C₁-C₅ alkyl;

wherein R₅ is

- (a) C₁-C₆ alkyl,
- (b) C₃-C₇ cycloalkyl,
- (c) aryl, or
- 15 (d) -Het;

wherein R₆ is

- (a) -(CH₂)_p-aryl, or
- (b) -(CH₂)_p-Het;

wherein R₇ is

- (a) C₁-C₅ alkyl,
- (b) amino C₁-C₄ alkyl.,
- (c) guanidinyl C₁-C₃ alkyl.,
- 25 (d) aryl, or
- (e) -Het;

wherein R₈ is

- (a) C₁-C₅ alkyl,
- (b) aryl, or
- 30 (c) -Het;

wherein R₁₀ is

- (a) hydrogen, or
- (b) C₁-C₅ alkyl;

wherein R₁₁ is -R;

35 wherein R₁₄ is

- (a) C₁-C₁₀ alkyl,
- (b) -(CH₂)_n-aryl,
- (c) -(CH₂)_n-Het, or

-81.

(d) (hydroxy-C₁-C₈ alkyl);
wherein R₂₁ is
(a) -NH₂, or
(b) -OH;
5 wherein R₂₂ is
(a) hydrogen, or
(b) C₁-C₃ alkyl;
wherein R₂₃ is
(a) aryl, or
10 (b) C₁-C₃ alkyl;
wherein i is zero to two, inclusive;
wherein m is one or two;
wherein for each occurrence n is independently an integer zero
to five, inclusive;
15 wherein p is zero to two, inclusive;
wherein Q is
(a) -CH₂-, or
(b) -CH(OH)-;
wherein M is -CO-;
20 wherein aryl is phenyl or naphthyl substituted by zero to 3 of
the following:
(a) C₁-C₃alkyl,
(b) hydroxy,
(c) C₁-C₃alkoxy,
25 (d) halo,
(e) amino,
(f) mono- or di-C₁-C₃alkylamino,
(g) -CHO,
(h) -COOH,
30 (i) COOR₂₅,
(j) CONHR₂₅,
(k) nitro,
(l) mercapto,
(m) C₁-C₃alkylthio,
35 (n) C₁-C₃alkylsulfinyl,
(o) C₁-C₃alkylsulfonyl,
(p) -N(R₄)-C₁-C₃alkylsulfonyl,
(q) SO₃H.

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(r) SO_2NH_2 ,

(s) -CN, or

(t) - CH_2NH_2 ;

wherein -Het is a 5- or 6-membered saturated or unsaturated ring containing from one to three heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur; and including any bicyclic group in which any of the above heterocyclic rings is fused to a benzene ring, which heterocyclic moiety is substituted with zero to 3 of the following:

10 (i) $\text{C}_1\text{-C}_6$ alkyl,
 (ii) hydroxy,
 (iii) trifluoromethyl,
 (iv) $\text{C}_1\text{-C}_4$ alkoxy,
 (v) halo,
 15 (vi) aryl,
 (vii) aryl- $\text{C}_1\text{-C}_4$ alkyl-,
 (viii) amino, or
 (ix) mono- or di- $\text{C}_1\text{-C}_4$ alkylamino;

with the overall provisos that

20 (1) when R_{14} is $\text{C}_1\text{-C}_3$ alkyl, $\text{E}_{10}\text{-F}_{11}$ does not include XL_6 , XL_{6a} , XL_{6e} or XL_{6f} ;
 (2) when R_{10} is $\text{C}_1\text{-C}_5$ alkyl, G_{121} or H_{131} must be present;
 (3) when X is $\text{R}_5\text{-CH}_2\text{-O-C(O)-}$ and only D_9 , E_{10} and F_{11} are present, R_5 is other than phenyl;
 25 or a carboxy-, amino-, or other reactive group-protected form thereof;
 or a pharmaceutically acceptable acid addition salt thereof.

8. A renin inhibitory peptide of claim 7

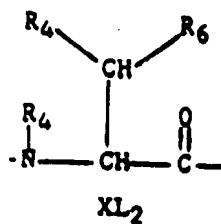
30 wherein X is

(a) $\text{R}_5\text{-O-CH}_2\text{-C(O)-}$,
 (b) $\text{R}_5\text{-CH}_2\text{-O-C(O)-}$,
 (c) $\text{R}_5\text{-}(\text{CH}_2)_n\text{-C(O)-}$,
 (d) $\text{R}_6\text{-}(\text{CH}_2)_1\text{-C(O)-}$, or
 35 (e) $[\text{R}_6\text{-}(\text{CH}_2)_n]_2\text{CH-C(O)-}$;

wherein A_6 is absent;wherein B_7 is absent;wherein C_8 is absent or a divalent moiety of the formula XL_2

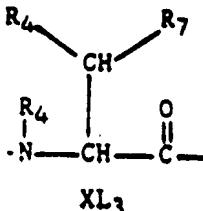
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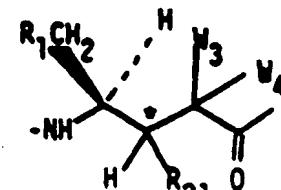
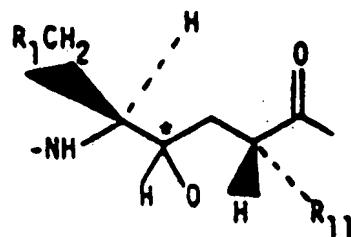
wherein D_9 is a divalent moiety of the formula XL_3

10

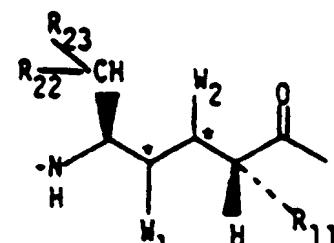
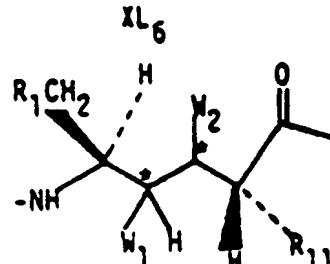


wherein $E_{10}\text{-}F_{11}$ is a divalent moiety of the formula XL_6 , XL_{6a} ,
15 XL_{6e} , XL_{6f} or XL_{6h}

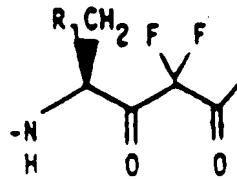
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wherein * indicates an asymmetric center which is either in the R or S configuration;

2310

98105708

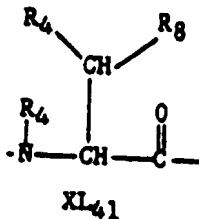
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wherein W_1 and W_2 are $\cdot\text{OH}$ or $\cdot\text{NH}_2$;

wherein W_3 and W_4 are $\cdot\text{H}$ or $\cdot\text{F}$;

wherein G_{121} is absent or a divalent moiety of the formula XL_{41}

5



10 wherein H_{131} is absent;

wherein I_{14} is absent;

wherein Z is $\cdot\text{N}(\text{R}_{10})(\text{OR}_{14})$;

wherein R is

- (a) isopropyl,
- (b) isobutyl,
- (c) phenylmethyl, or
- (d) $-(\text{CH}_2)_p\text{-C}_3\text{-C}_7$ cycloalkyl;

wherein R_1 is

- (a) $\text{C}_1\text{-C}_5$ alkyl,
- (b) aryl, or
- (c) $\text{C}_3\text{-C}_7$ cycloalkyl;

wherein R_4 at each occurrence is the same or different and is

- (a) hydrogen, or
- (b) $\text{C}_1\text{-C}_5$ alkyl;

25 wherein R_5 is

- (a) $\text{C}_1\text{-C}_6$ alkyl,
- (b) $\text{C}_3\text{-C}_7$ cycloalkyl,
- (c) aryl, or
- (d) $\cdot\text{Het}$;

30 wherein R_6 is

- (a) $-(\text{CH}_2)_p\text{-aryl}$, or
- (b) $-(\text{CH}_2)_p\text{-Het}$;

wherein R_7 is

- (a) $\text{C}_1\text{-C}_5$ alkyl,
- (b) amino $\text{C}_1\text{-C}_4$ alkyl-,
- (c) guanidinyl $\text{C}_1\text{-C}_3$ alkyl-,
- (d) aryl, or
- (e) $\cdot\text{Het}$;

.92.

wherein R₈ is

- (a) C₁-C₅ alkyl,
- (b) aryl, or
- (c) -Het;

5 wherein R₁₀ is

- (a) hydrogen, or
- (b) C₁-C₅ alkyl;

wherein R₁₁ is -R;

wherein R₁₄ is

10

- (a) C₁-C₁₀ alkyl,
- (b) -(CH₂)_n-aryl,
- (c) -(CH₂)_n-Het, or
- (d) (hydroxy-C₁-C₈ alkyl);

wherein R₂₁ is

15

- (a) -NH₂, or
- (b) -OH;

wherein R₂₂ is

- (a) hydrogen, or
- (b) C₁-C₃ alkyl;

20 wherein R₂₃ is

- (a) aryl, or
- (b) C₁-C₃ alkyl;

wherein i is zero to two, inclusive;

25 wherein for each occurrence n is independently an integer of zero to five, inclusive;

wherein p is zero to two, inclusive;

wherein aryl is phenyl or naphthyl substituted by zero to 3 of the following:

30

- (a) C₁-C₃alkyl,
- (b) hydroxy,
- (c) C₁-C₃alkoxy,
- (d) halo,
- (e) amino,
- (f) mono- or di-C₁-C₃alkylamino,

35

- (g) -CHO,
- (h) -COOH,
- (i) COOR₂₅,
- (j) CONHR₂₅.

.9^.

- (k) nitro,
- (l) mercapto,
- (m) $C_1\text{-}C_3$ alkylthio,
- (n) $C_1\text{-}C_3$ alkylsulfinyl,
- 5 (o) $C_1\text{-}C_3$ alkylsulfonyl,
- (p) $\text{-N}(R_4)\text{-}C_1\text{-}C_3$ alkylsulfonyl,
- (q) SO_3H ,
- (r) SO_2NH_2 ,
- (s) -CN , or
- 10 (t) -CH_2NH_2 ;

wherein -Het is a 5- or 6-membered saturated or unsaturated ring containing from one to three heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur; and including any bicyclic group in which any of the above heterocyclic rings is fused 15 to a benzene ring, which heterocyclic moiety is substituted with zero to 3 of the following:

- (i) $C_1\text{-}C_6$ alkyl,
- (ii) hydroxy,
- (iii) trifluoromethyl,
- 20 (iv) $C_1\text{-}C_4$ alkoxy,
- (v) halo,
- (vi) aryl,
- (vii) aryl- $C_1\text{-}C_4$ alkyl-,
- (viii) amino, or
- 25 (ix) mono- or di- $C_1\text{-}C_4$ alkylamino;

with the overall provisos that

- (1) when R_{14} is $C_1\text{-}C_3$ alkyl, $E_{10}\text{-}F_{11}$ does not include XL_6 , XL_{6a} , XL_{6e} or XL_{6f} ;
- (2) when R_{10} is $C_1\text{-}C_5$ alkyl, G_{121} must be present;
- 30 (3) when X is $R_5\text{-}CH_2\text{-}O\text{-}C(O)\text{-}$ and only D_9 , E_{10} and F_{11} are present, R_5 is other than phenyl;
- or a carboxy-, amino-, or other reactive group-protected form thereof;
- or a pharmaceutically acceptable acid addition salt thereof.

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9. Boc-Phe-His-Sta-Ile-NHOCH₂-phenyl, or L-Histidinamide, N-[(1,1-dimethylethoxy)carbonyl]-L-phenylalanyl-N-[2-hydroxy-4-[(2-methyl-1-[(phenylmethoxy)amino]carbonyl]butyl]amino]-1-(2-methylpropyl)-4-

- 34 -

oxobutyl]-, [1S-[1R*,2R*,4(1R*,2R)]]-, a compound of claim 8.

10. Boc-Phe-His-Sta-Ile-NHOCH₃, or L-Histidinamide, N-[(1-dimethyl-ethoxy)carbonyl]-L-phenylalanyl-N-[2-hydroxy-4-[[[-(methoxyamino)carbonyl]-2-methylbutyl]amino]-1-(2-methylpropyl)-(4-oxobutyl]-, [1S-[1R*,2R*,4(1R*,2R*)]]-, a compound of claim 8.

11. Boc-Phe-His-Sta-Ile-NHOC₂H₅, or L-Histidinamide, N-[(1,1-dimethylethoxy)carbonyl]-L-phenylalanyl-N-[4-[[1-[(ethoxyamino)carbonyl]-2-methylbutyl]amino]-2-hydroxy-1-(2-methylpropyl)-4-oxobutyl]-, [1S-[1R*,2R*,4(1R*,2R*)]]-, a compound of claim 8.

12. Boc-Phe-His-Sta-Ile-NHO-phenyl, or L-Histidinamide, N-[(1,1-dimethylethoxy)carbonyl]-L-phenylalanyl-N-[2-hydroxy-4-[[2-methyl-1-phenoxyamino)carbonyl]butyl]amino]-1-(2-methylpropyl)-4-oxobutyl]-, [1S-[1R*,2R*,4(1R*,2R*)]]-, a compound of claim 8.

13. Boc-Phe-His-Sta-Ile-NHO-(p-nitrobenzyl), or L-Histidinamide, N-[(1,1-dimethylethoxy)carbonyl]-L-phenylalanyl-N-[2-hydroxy-4-[[2-methyl-1-[[[(4-nitrophenyl)methoxy]amino]carbonyl]butyl]amino]-1-(2-methoxypropyl)-4-oxobutyl]-, [1S-[1R*,2R*,4(1R*,2R*)]]-, a compound of claim 8.

14. Boc-Phe-His-LVA-Ile-NHOCH₂-phenyl, or L-Histidinamide, N-[(1,1-dimethylethoxy)carbonyl]-L-phenylalanyl-N-[2-hydroxy-5-methyl-4-[[[2-methyl-1-[[[(phenylmethoxy)amino]carbonyl]butyl]amino]carbonyl]-1-(2-methylpropyl)hexyl]-, [1S-[1R*,2R*,4R*(1R*,2R*)]]-, a compound of claim 8.